ORGANIC AND BIOLOGICAL CHEMISTRY

[Contribution from the Department of Chemistry of the University of California at Los Angeles, Los Angeles 24, Calif.]

Studies in Stereochemistry. XXXII. Models for 1,2-Asymmetric Induction[1]

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The effect of solvent, reagent and temperature on stereospecificity and steric direction has been investigated in the synthesis of 2,3-diphenyl-2,3-butanediols from 1,2-diphenyl-2-hydroxy-1-propanone and 3-hydroxy-3-phenyl-2-butanone, and in the synthesis of 2,3-diphenyl-3-methoxy-2-butanols from 1,2-diphenyl-2-methoxy-1-propanone and 3-methoxy-3-phenyl-2-butanone. The results have been interpreted on the basis of cyclic, open-chain and dipolar models which control conformation and the balance of products. Appropriate manipulation of structural and environmental factors can produce results in conformity with expectations based on any one of the three models.
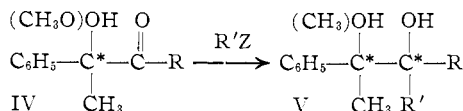
Initial studies[3] established the applicability of an open-chain model (I) to correlate and predict the predominant steric direction of addition reactions to carbonyl groups adjacent to asymmetric centers in noncyclic systems. A later investigation[4] established that in systems where an open-chain (I) and cyclic
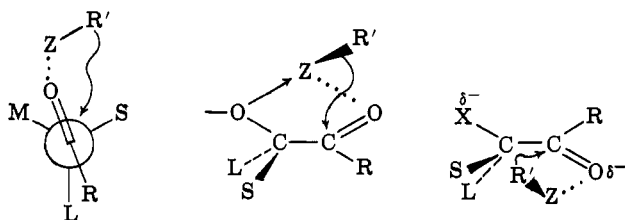
I, open-chain model   II, cyclic model   III, dipolar model

Transition states of lowest energy

model (II) were pitted against one another, the cyclic model predicted the stereochemical outcome. While the present investigation was in progress, others[5] confirmed the importance of the cyclic model, but also observed that in certain special cases in the same system, the cyclic model did not apply. Other exceptions to the applicability of the open-chain model had been observed in the kinetically controlled Meerwein–Ponndorf reduction of ketones,[3e] and particularly in 1,2-addition reactions of α-chlorocarbonyl compounds.[6] The latter results were convincingly rationalized on the basis of a dipolar model (III).

The present investigation was undertaken to identify those structural and medium factors which channel the results into correlation with each of the three models. Systems represented by general structures IV and V were selected for several reasons: (1) Under certain sets of conditions with these systems, results predicted by any of the three models can be envisioned.

(2) Configurations of products and methods for their analysis had been previously established.[4]

Results

Table I records the reaction conditions, yields and ratios of *meso-* and (±)-diastereomers formed in the synthesis of the diastereomeric 2,3-diphenyl-2,3-butanediols from 1,2-diphenyl-2-hydroxy-1-propanone.[7]

Table I

Reaction Conditions, Yields and Ratios of *meso-* and (±)-Diastereomers Formed in Synthesis of 2,3-Diphenyl-2,3-butanediols from (±)-1,2-Diphenyl-2-hydroxy-1-propanone at 0°

Run	Solvent system	Reagent	Yld., %	Ratio diast.[a] meso/(±)
1[b]	Pentane	CH_3Li	88	3.4
2[c]	Ether	CH_3Li	74	11
3[b]	Ether	CH_3Li	100	8
4	Ether + TMEDA[d]	CH_3Li	100	3.3
5	Ether	75% $(CH_3)_2Mg$ / 25% $(CH_3)_2Mg \cdot MgBr_2$	85	3.5
6[e]	Tetrahydrofuran	94% $(CH_3)_2Mg$ / 6% $(CH_3)_2Mg \cdot MgBr_2$	90	6
7	Ether + TMEDA[d]	$(CH_3)_2Mg \cdot MgBr_2$	68	4.6
8[c]	Ether	$(CH_3)_2Mg \cdot MgI_2$	61	2.0
9	Ether	$(CH_3)_2Mg \cdot MgBr_2$	70	2.7
10[b]	Ether	$(CH_3)_2Mg \cdot MgBr_2$	102	3.0
11[b]	Ether	$(CH_3)_2Mg \cdot MgCl_2$	56	2.9
12[e]	Tetrahydrofuran	$(CH_3)_2Mg \cdot MgBr_2$	96	10
13	Tetrahydrofuran	$(CH_3)_2Mg \cdot 1.5MgBr_2$	92	5
14	Dimethoxyethane	$(CH_3)_2Mg \cdot MgBr_2$	100	3.2
15	Dimethoxyethane + TMEDA[d]	$(CH_3)_2Mg \cdot MgBr_2$	86	5

[a] Cyclic model predicts ratio >1, open-chain and dipolar models <1. [b] Taken from data of Stocker, Sidisunthorn, Benjamin and Collins; ref. 5. [c] Taken from data found in ref. 4. [d] Tetramethylethylenediamine. [e] Results of runs 6 and 12 are within experimental error of one another.

Table II provides similar data for synthesis of the same diastereomers from 3-hydroxy-3-phenyl-2-butanone. In Table III are found the results of the synthesis of the diastereomers of 2,3-diphenyl-3-methoxy-2-butanol from 1,2-diphenyl-2-methoxy-1-propanone and, in Table IV, from 3-methoxy-3-phenyl-2-butanone. Of the 47 runs listed, 17 of them are taken from previous work,[4,5] and are included for purposes of comparison. The small overlap between our results and those of Collins, *et al.*,[5] serves to test the methods of diastereomer analysis. The isotope dilution method used by these authors is more accurate than our infrared method, and the results gained by the two methods are the same within experimental error.

(1) This work was in part supported by the U. S. Army Research Office (Durham).

(2) N.S.F. Predoctoral Fellow, 1959–1961.

(3) (a) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); (b) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952); (c) F. A. Abd Elhafez and D. J. Cram, *ibid.*, **74**, 5846 (1952); (d) D. J. Cram, F. A. Abd Elhafez and H. Weingerten, *ibid.*, **75**, 2293 (1953); (e) D. J. Cram and F. D. Greene, *ibid.*, **75**, 6005 (1953); (f) D. J. Cram, F. A. Abd Elhafez and H. L. Nyquist, *ibid.*, **76**, 22 (1954); (g) D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954); (h) D. J. Cram and J. E. McCarty, *ibid.*, **76**, 5740 (1954).

(4) D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2737 (1959).

(5) J. H. Stocker, D. Sidisunthorn, B. M. Benjamin and C. J. Collins, *ibid.*, **82**, 3913 (1960).

(6) J. W. Cornforth, R. H. Cornforth and K. K. Mathews, *J. Chem. Soc.*, 112 (1959).

(7) Methods of analysis of products are set forth in Experimental.

TABLE II

REACTION CONDITIONS, YIELDS AND RATIOS OF *meso-* AND ($\pm$)-DIASTEREOMERS FORMED IN SYNTHESIS OF 2,3-DIPHENYL-2,3-BUTANEDIOLS FROM ($\pm$)-3-HYDROXY-3-PHENYL-2-BUTANONE

Run	Solvent system	Reagent	Yld., %	Ratio diast.[a] ($\pm$)/ meso
16[b]	Pentane	C_6H_5Li	76	5.0
17[c]	Ether	C_6H_5Li	92	7
18[b]	Ether	C_6H_5Li	100	10
19	Ether + TMEDA[d]	C_6H_5Li	55	4
20	Ether	$(C_6H_5)_2Mg$	25	1.8
21	Ether	$(C_6H_5)_2Mg$	58	1.8
22[b]	Ether	$(C_6H_5)_2Mg$	41	2.2
23	Tetrahydrofuran	$(C_6H_5)_2Mg$	48	1.6
24	Ether + TMEDA[d]	$(C_6H_5)_2Mg \cdot MgBr_2$	38	2.7
25[b]	Ether	$(C_6H_5)_2Mg \cdot MgI_2$	56	2.0
26[b]	Ether	$(C_6H_5)_2Mg \cdot 2.5MgI_2$	52	1.7
27	Ether	$(C_6H_5)_2Mg \cdot MgBr_2$	78	0.56
28[b]	Ether	$(C_6H_5)_2Mg \cdot MgBr_2$	93	.42
29[b]	Ether	$(C_6H_5)_2Mg \cdot 3.5MgBr_2$	76	.44
30[b]	Ether	$(C_6H_5)_2Mg \cdot MgCl_2$	81	.3
31	Tetrahydrofuran	$(C_6H_5)_2Mg \cdot MgBr_2$	52	1.4
32	Tetrahydrofuran	$(C_6H_5)_2Mg \cdot 1.5MgBr_2$	61	1.7
33	Dimethoxyethane	$(C_6H_5)_2Mg \cdot MgBr_2$	90	1.3
34	Dimethoxyethane + TMEDA[d]	$(C_6H_5)_2Mg \cdot MgBr_2$	47	1.3
35	Ether[e]	$(C_6H_5)_2Mg \cdot MgBr_2$	60	0.77
36	Ether[e]	$(C_6H_5)_2Mg$	46	2.7

[a] Cyclic model predicts ratio >1, open-chain and dipolar model <1. [b] Taken from data in ref. 5. [c] Taken from data in ref. 4. [d] Tetramethylethylenediamine. [e] Reactions run at $-30°$; all other reactions run at $0°$.

TABLE III

REACTION CONDITIONS, YIELDS AND RATIOS OF *erythro-* TO *threo-*DIASTEREOMERS FORMED IN SYNTHESIS OF 2,3-DIPHENYL-3-METHOXY-2-BUTANOLS FROM ($\pm$)-1,2-DIPHENYL-2-METHOXY-1-PROPANONE AT $0°$

Run	Solvent sytem	Reagent	Yld., %	Ratio diast.[a] erythro/ threo
37[b]	Ether	CH_3Li	92	2
38	Ether	$(CH_3)_2Mg \cdot MgBr_2$	100	2
39	Ether	94% $(CH_3)_2Mg$ 6% $(CH_3)_2Mg \cdot MgI_2$	100	1.7
40	Ether + TMEDA	$(CH_3)_2Mg \cdot MgBr_2$	100	0.44
41	Tetrahydrofuran	$(CH_3)_2Mg \cdot MgBr_2$	100	1.2
42	Tetrahydrofuran	94% $(CH_3)_2Mg$ 6% $(CH_3)_2Mg \cdot MgI_2$	100	1.1

[a] Cyclic model predicts ratio >1; open-chain and dipolar models. <1. [b] Results taken from ref. 4.

TABLE IV

REACTION CONDITIONS, YIELDS AND RATIOS OF *threo* TO *erythro-*DIASTEREOMERS FORMED IN SYNTHESIS OF 2,3-DIPHENYL-3-METHOXY-2-BUTANOLS FROM ($\pm$)-3-METHOXY-3-PHENYL-2-BUTANONE AT $0°$

Run	Solvent system	Reagent	Yld., %	Ratio diast.[a] threo/ erythro
43[b]	Ether	C_6H_5Li	78	9
44	Ether	$(C_6H_5)_2Mg$	96	7
45	Ether	$(C_6H_5)_2Mg \cdot MgBr_2$	49	6
46	Ether + TMEDA	$(C_6H_5)_2Mg \cdot MgBr_2$	56	13
47	Tetrahydrofuran	$(C_6H_5)_2Mg \cdot MgBr_2$	78	19
48	Tetrahydrofuran	$(C_6H_5)_2Mg$	64	13

[a] Cyclic model predicts ratio >1; open-chain and dipolar models, <1. [b] Results taken from ref. 4.

The reactions were carried out at $0°$ unless otherwise specified, and a 10-to-20 mole excess of organometallic

reagent was used. In the reactions involving TMEDA (tetramethylethylenediamine) a two-to-one molar ratio of diamine to organometallic reagent was employed, the presumption being that the reagent could coördinate not more than 4 nitrogens. The Grignard reagents used in dimethoxyethane and tetrahydrofuran were prepared in ether and then transferred to the desired solvent. Description of the manipulation of the Grignard reagent composition and its analysis are found in the Experimental.

Discussion

Comparison of Reactions Leading to 2,3-Diphenyl-2,3-butanediols and to 2,3-Diphenyl-3-methoxy-2-butanols.—Marked differences are found in the behavior of the α-hydroxy and α-methoxy ketones used in the addition reactions. The α-hydroxy ketones are first converted to alkoxides which in this state enter into the addition reaction. The highly negative α-oxygen of the alkoxides coupled with the polarized oxygen of the carbonyl group should make the five-membered ring of the cyclic model particularly stable. On the other hand, the dipole–dipole interactions of the two carbon–oxygen bonds would tend to stabilize the *trans* conformation found in the dipolar model. Of the two models, the cyclic is the more compressed, and its stability the most subject to steric effects. In all systems, the cyclic and dipolar models predict opposite results, and the delicate balance between the two should be subject to many effects. The open-chain model probably does not seriously compete with the other two in the α-hydroxy ketone type of system.

With α-methoxy ketones as substrates, the competition is probably mainly between the cyclic and open-chain models, which predict opposite results. The cyclic model should be more subject to steric effects than the open-chain, and again the balance between the two models should be subject to variation.

Application of Models to Synthesis of 2,3-Diphenyl-2,3-butanediols.—All of the results obtained with alkyl- or aryllithium reagents (runs 1–4 and 16–19) conform to those predicted by cyclic models VI and VII. The runs made in ether as solvent without added tetramethylethylenediamine (TMEDA) gave higher
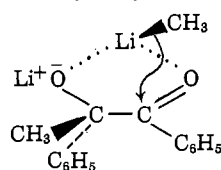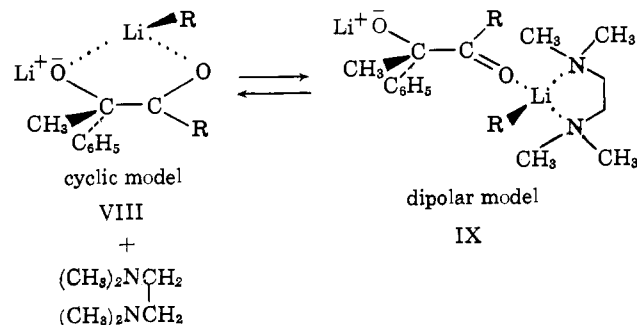

VI (*meso* dominates by factors of 3 to 10)
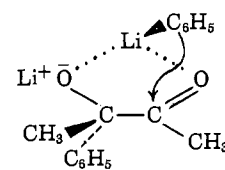
VII (($\pm$) dominates by factors of 4–8)

stereospecificities, whereas those run in pentane, or in ether with added TMEDA, gave lower specificities.[8] Thus proper selection of medium can vary the diastereomer ratio by factors of 2 to 3.

cyclic model

VIII

+

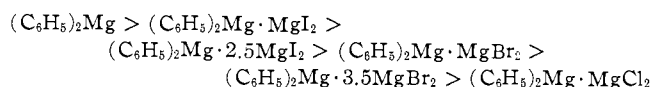$(CH_3)_2N\overset{|}{C}H_2$

$(CH_3)_2NCH_2$

dipolar model

IX

(8) Cram and Kopecky (ref. 4) mistakenly in Table II and again in the text on page 2751 referred to these reactions actually run in ether as being run in pentane.

The lowering of the stereospecificity with added TMEDA suggests competition between substrate and TMEDA for coördination with the lithium. To the extent that the coördination sites of lithium are unavailable to the oxygen of the substrate, the cyclic model would not apply, and the dipolar model would contribute. The different specificity in ether and pentane as solvents is attributed to the fact that organolithium reagents exist in pentane as aggregates of many molecules, and as dimers in ether.[9] The larger steric requirements of the aggregates would increase the contribution of the dipolar model. Another effect would be the increase in importance of dipole–dipole interactions in the substrate in passing from ether to pentane, which would increase the importance of the dipolar model and would decrease stereospecificity.
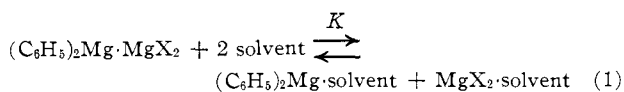
The effect of solvent with dialkyl- and diarylmagnesium as reagent can be seen in the results of runs 5, 6, 7 (Table I) and 20–24 (Table II). In runs 7 and 24 in which TMEDA was added, the dense white precipitate that separated was presumed to be the complex of magnesium bromide–TMEDA. The reagent was probably more free of halide in these than in the other reactions. In those reactions involving dimethylmagnesium, the product predicted by the cyclic model dominated by factors that varied only between 3.5 and 5.7 in going from ether to tetrahydrofuran. With diphenylmagnesium, the cyclic model's product exceeded the others by factors that ranged from 1.8 to 1.6 with the same solvent change. Clearly these reactions are less stereospecific than those that involve the lithium reagents, possibly because the steric requirements for the cyclic model are more compatible with lithium than with magnesium. The fact that dimethylmagnesium is more stereospecific than the diphenylmagnesium reagent also points toward a steric requirement for formation of the five-membered ring.

The presence of magnesium halides not only affects the stereospecificity but in some cases even the steric direction. With dimethylmagnesium the effect is small (compare run 5 with runs 8–11 of Table I), but with diphenylmagnesium in the presence of magnesium bromide or chloride, the cyclic model predicts the wrong result[5] (runs 21–30, Table II). Thus a graded series is observed in which the ratio $meso/(\pm)$ decreases and varies by a factor of 7. The cyclic model predicts

$(C_6H_5)_2Mg > (C_6H_5)_2Mg \cdot MgI_2 >$
$\qquad (C_6H_5)_2Mg \cdot 2.5MgI_2 > (C_6H_5)_2Mg \cdot MgBr_2 >$
$\qquad\qquad (C_6H_5)_2Mg \cdot 3.5MgBr_2 > (C_6H_5)_2Mg \cdot MgCl_2$

the correct result with diphenylmagnesium by a factor of 2.2 at one extreme. The dipolar model predicts the correct result with diphenylmagnesium–magnesium chloride by a factor of 3.3 at the other.

An interpretation of these results is as follows. The balance of products is determined by the relative energies of the transition states of the two models. The transition state of the cyclic model is too confined to accommodate readily the magnesium halide, whereas the dipolar model is less subject to steric effects. Thus operation of the cyclic model depends on solvent being able to complex competitively the magnesium halide without raising the energy of the system. A measure of this ability would be found in the value of the equilibrium constant for eq. 1.[10] As the value of K in-

$$(C_6H_5)_2Mg \cdot MgX_2 + 2\ \text{solvent} \underset{\xleftarrow{\hspace{1cm}}}{\overset{K}{\xrightarrow{\hspace{1cm}}}}$$
$$(C_6H_5)_2Mg \cdot \text{solvent} + MgX_2 \cdot \text{solvent} \quad (1)$$

creases, the cyclic model would be more favored. The value of K would depend on both the characters of the halide and of the solvent. Possibly as X is changed from iodide to bromide to chloride, the value of K decreases, and the energy of the cyclic model increases accordingly, in conformity with observation. This interpretation is supported by the fact that a shift from ether to the more polar tetrahydrofuran or dimethoxyethane as solvent (runs 31–33, $(C_6H_5)_2Mg \cdot MgBr_2$ as reagent) shifts the steric outcome from that consistent with the dipolar models to that consistent with the cyclic model.

A comparison of the results of runs 35 and 36 with those of runs 27 and 21 (Table II), respectively, indicates that a lowering of reaction temperature from 0° to −30° has only a minor effect on the stereochemical outcome of the reaction.

Application of Models to Synthesis of 2,3-Diphenyl-3-methoxy-2-butanols.

The stereospecificity of these reactions (Tables III and IV) varies less with the nature of the organometallic reagent than in the reactions leading to the diols. In ether, methyllithium, dimethylmagnesium and dimethylmagnesium–magnesium iodide (runs 37–39, Table III) give approximately the same results, as do phenyllithium, diphenylmagnesium and diphenylmagnesium–magnesium bromide (runs 43–45, Table IV).

All of the results conform to those expected of the cyclic model except run 40 (Table III), in which TMEDA was added to an ether solution of dimethylmagnesium–magnesium bromide. The presence of the diamine changed the *erythro/threo* ratio from 1.7 to 0.44, or to a ratio of products predicted by the open-chain model. Possibly in this system, substrate and TMEDA are competing for the organometallic reagent, and the more basic species, the amine, is favored. The complexed organometallic then reacts with substrate *via* the open-chain model. The fact that diphenylmagnesium–magnesium bromide does not show the same sensitivity to TMEDA (compare runs 45 and 46, Table IV) probably is associated with the increased size of the arylmetallic reagent. The complex with substrate is less compressed than the complex with TMEDA, and therefore the former is favored with the diarylmetallic reagent.

In these interpretations, the cyclic models from the α-hydroxy ketones would appear much more subject to steric effects than those which involve the α-methoxy ketones. This effect is attributed to the presence of two metals with their ligands in the α-hydroxy ketone models as compared with one metal with its ligands in the α-methoxy ketone models.

Experimental

Starting Materials.—The substance 3-hydroxy-3-phenyl-2-butanone was prepared in 42% yield,[11] and 1,2-diphenyl-2-hydroxy-1-propanone[12] in 84% yield, mp. 67–68°. Racemic 1,2-diphenyl-2-methoxy-1-propanone was prepared[4] in 39% yield, b.p. 150–151° (5 mm.), n^{25}D 1.5694. The method of preparation of 3-methoxy-3-phenyl-2-butanone previously reported[4] gave variable results, so the following method was developed.

To 9.4 g. of sodium hydride in 300 ml. of dry dioxane under an atmosphere of dry nitrogen was added, with stirring over a period of 3 hr., 42 g. of 2-hydroxy-2-phenyl-1-propanone in 100 ml. of dry dioxane. The mixture was stirred for 20 hr., and 100 g. of methyl iodide was added slowly, and stirring was continued for 20 hr. After 20 ml. of methanol had been added dropwise, the mixture was shaken with 1 liter of water and 250 ml. of pentane. The pentane solution was washed with water, dried and

(9) (a) E. Warhurst, *Discussions Faraday Soc.*, **2**, 239 (1947); (b) M. T. Rogers and T. L. Brown, *J. Phys. Chem.*, **61**, 366 (1957); (c) T. L. Brown and M. T. Rogers, *J. Am. Chem. Soc.*, **79**, 1859 (1957); (d) G. Wittig, F. J. Meyer and G. Lange, *Ann.*, **571**, 184 (1951).

(10) R. E. Dessy, G. S. Handler, J. H. Wotiz and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957).

(11) J. Wegmann and H. Dahn, *Helv. Chim. Acta*, **29**, 101 (1946).

(12) L. Mehr, E. Becker and P. Spoerri, *J. Am. Chem. Soc.*, **77**, 984 (1955).

evaporated and the product was distilled to give 34.8 g. of a fraction, b.p. 60–81° (0.5 mm.). The distillate was redistilled through a spinning band column to give 22.0 g. of product whose infrared spectrum was free of absorption in the hydroxyl region; b.p. 92.5–93.0° (8 mm.), n^{25}D 1.5093.

Standards for Infrared Analyses.—Pure samples of (±)- and meso-1,2-diphenyl-1,2-butanediol were available from previous studies.[4] Recrystallization of a slightly impure sample of (+)-erythro-2,3-diphenyl-3-methoxy-2-butanol[4] from pentane gave dense white cubes, m.p. 92.5–93.4°, $[\alpha]^{25}$D +13.4° (chloroform, c 5). Racemic (±)-threo-2,3-diphenyl-3-methoxy-2-butanol was prepared in a pure state.

A solution of phenyllithium in ether was prepared in the usual way from 31.4 g. of bromobenzene and 2.8 g. of lithium. To an aliquot (100 ml.) of the solution which contained 0.10 mole of phenyllithium was added under pure nitrogen with stirring at 0°, 11.5 g. of racemic 3-methoxy-3-phenyl-2-butanone in 100 ml. of dry ether. The reaction mixture was stirred for 2 hr. at 25°, cooled to 0°, and 24 g. of 3,5-dinitrobenzoyl chloride in 250 ml. of anhydrous ether was added slowly with vigorous stirring. After addition was complete, the mixture was held at reflux for 8 hr., cooled and mixed with 500 ml. of cold water. The resulting emulsion was shaken with 500 ml. of water and 1250 ml. of ether; the ether layer was washed with 1 N sodium bicarbonate solution and again with water. The ether layer was dried, filtered, and the solvent was evaporated. The partially crystalline residue was chromatographed on 1100 g. of neutral, activated alumina made up in pentane. After the column had been well washed with pentane, the desired ester was eluted with 1 liter of a 50–50 ether–pentane mixture. Six recrystallizations of the ester from 70% carbon tetrachloride–30% hexane gave 7.0 g. (24%) of pale yellow crystals, m.p. 166–167°.

Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 63.99; H, 4.92; N, 6.22; Found: C, 64.12; H, 4.96; N, 6.37.

To a dry solution of the above 3,5-dinitrobenzoate of (±)-threo-2,3-diphenyl-3-methoxy-2-butanol in 125 ml. of tetrahydrofuran was added with stirring 3.0 g. of lithium aluminum hydride. To the resulting red solution was added an additional 25 ml. of tetrahydrofuran. The solution was held at reflux for 2 hr., cooled to 0° and hydrolyzed with cold water. The reaction mixture was acidified with dilute sulfuric acid and extracted with pentane. The pentane extract was washed with 0.5 N sodium carbonate solution, with water, and was dried and evaporated, and the 3.58 g. of liquid was chromatographed on 375 g. of neutral, activated alumina. The column was eluted with a 50–50 ether–pentane solution to give 3.1 g. (93%) of product, m.p. 53–55°. This material was recrystallized from 20% aqueous methanol to give 1.9 g. of product, m.p. 56.5–57.5°. An infrared spectrum of this material was identical with that of an authentic sample of pure (−)-threo-2,3-diphenyl-3-methoxy-2-butanol.[4]

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.69; H, 7.81. Found: C, 79.63; H, 7.89.

Purification of Solvents.—Technical grade TMEDA, 300 g., was dried over potassium hydroxide pellets and then refluxed for 2 hr. with 50 g. of n-butyric anhydride to remove primary and secondary amines. The mixture was distilled and 278.3 g., b.p. 118–122 (760 mm.), of material collected. The distillate was then held at reflux for 24 hr. over fresh potassium hydroxide pellets and redistilled through a bubble plate column under a head of dry nitrogen; b.p. 122° (760 mm.), n^{25}D 1.4153.

Ether and tetrahydrofuran were dried by distilling them from lithium aluminum hydride directly into the flask in which they were to be used. Dimethoxyethane was purified by passage through activated alumina and distillation from lithium aluminum hydride.

Preparation and Analyses of Organometallic Solutions.—Approximately molar solutions of methylmagnesium iodide, bromide and phenylmagnesium bromide were prepared in 500 ml. of anhydrous ether in the usual way. Precipitates were allowed to settle. From the clear solutions, 10-ml. aliquots were withdrawn, hydrolyzed with 25 ml. of cold water and analyzed for base[13] with nitric acid as standard, and for halide by the Volhard method[14] for halogen.

Solutions of the above Grignard reagent in dimethoxyethane were prepared by solvent transfer as follows. Approximately 100-ml. aliquots (0.1 mole) of each Grignard reagent were transferred to dry flasks under dry pure nitrogen. To each of the aliquots an equal volume of pure dimethoxyethane was added. The ether was distilled through a 40-cm. Vigreux column until nothing distilled at a pot temperature of 95°. A large amount of white precipitate formed with both the bromide and iodide Grignard complexes. After the solid had settled, aliquots of clear solution were then analyzed for base[13] and halide.[14]

(13) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1945, p. 94.

(14) W. W. Scott, "Standard Methods of Chemical Analysis," 5th Ed., Vol. 1, D. Van Nostrand Co., Inc., New York, N. Y., 1939, pp. 192 and 457.

In reactions carried out in tetrahydrofuran, the organometallic was prepared in ether, insoluble material allowed to settle, the clear solution evaporated under reduced pressure and pure tetrahydrofuran added.

The organolithium reagents were prepared in ether by the ordinary method, solids allowed to settle, and the clear liquid filtered through a plug of glass wool.

Phenyllithium was assayed in several solutions by adding a small amount of the organolithium solution to 2-ml. portions of 1% 9-methylfluorene in diethyl ether. A bright red color is produced if phenyllithium is present. To a solution of 1 N phenyllithium in ether was added an equal volume of dimethoxyethane. No loss of intensity of color in the above test could be detected. However, after removal of diethyl ether under reduced pressure at room temperature (2 hr.) no red color could be detected in the test.

The diphenylmagnesium solutions were prepared as follows. To a 400-ml. ethereal solution 1 N in phenylmagnesium bromide was added slowly with vigorous stirring at reflux temperature 46.9 g. of dioxane (1.33 mole ratio to Grignard reagent). The resulting mixture was held at reflux for 4 hr. and allowed to settle 10 hr. The solvent was removed from a 100-ml. aliquot of the clear liquid under reduced pressure at elevated temperature. About 60 ml. of solvent was then added to the dried aliquot.

The dimethylmagnesium solutions were prepared by exchanging solvent in a 1 N ethereal solution of the methyl Grignard reagent with an equal volume of dimethoxyethane. Solvent was then removed from clear 100-ml. aliquots of dimethoxyethane solution and 60 ml. of the desired solvent added.

TABLE V

ANALYSIS OF GRIGNARD REAGENTS

	$(CH_3)_2$- Mg·MgI₂		$(CH_3)_2$- Mg·MgBr₂		$(C_6H_5)_2$- Mg·MgBr₂	
	Ether	DME[a]	Ether	DME[a]	Ether	DME[a]
Base concn. (M)	0.95	0.99	0.91	0.76	0.78	1.37
Halide concn. (M)	.97	0.06	.93	0.19	.82	1.29
Ratio R_2Mg/MgX_2[b]	.98	17	.98	4.0	.95	1.06
% R_2Mg free of MgX_2	0	94	0	75	0	6

[a] Dimethoxyethane. [b] In solution.

In the reactions where additional magnesium bromide was used, the magnesium bromide was made from magnesium and hydrogen bromide in anhydrous ether. Into 60 ml. of dry ether over 1.2 g. of magnesium was bubbled anhydrous hydrogen bromide gas. Addition of the gas was stopped just prior to complete disappearance of magnesium. The ether was distilled, and the mixture stopped boiling when the upper phase disappeared and did not boil at less than 90°. Another 50 ml. of ether was added and distilled to remove any hydrogen bromide. The last traces of ether were removed under reduced pressure of 30°, 25 ml. of ether was again added, and the solvent again removed under reduced pressure. To the resulting dried solid (0.05 mole) of magnesium bromide was added the desired organometallic solution.

Reactions Leading to 2,3-Diphenyl-2,3-butanediols.—All reactions were carried out on 1.0 g. of carbonyl compound in 25 ml. of the reaction solvent under a pure nitrogen atmosphere. The organometallic reagent (10 to 20 moles per mole of carbonyl compound) dissolved in 50 to 75 ml. of reaction solvent was added dropwise to the rapidly stirred ketone held at 0°. The reaction mixture was stirred for 2 additional hr. at 0°. Reaction mixtures that involved lithium reagents were hydrolyzed with ice followed by just enough cold dilute sulfuric acid to dissolve the solids. To the reactions in which ether was not the solvent, 50 ml. of ether was added and the layers separated, and the aqueous layer was washed with 30 ml. of ether. The combined layers were washed with dilute sodium bicarbonate, water, then dried and evaporated to oils. The reactions that involved Grignard reagents were hydrolyzed with a cold saturated solution of ammonium chloride and worked up in the manner just described.

In runs 4, 5, 19 and 27, a 50-ml. aliquot of 1 N organometallic reagent made in the customary manner on a 0.5 M scale was used. In the reactions where TMEDA was added to ether (runs 4, 7, 19 and 24), 11.6 g. (0.10 mole) of TMEDA was added to a 50-ml. aliquot of 1 N organometallic reagent. Where TMEDA was added to the runs in dimethoxyethane (runs 15 and 35), 17.4 g. (0.15 mole) of TMEDA has added to the dimethoxyethane solution containing 0.075 mole of organometallic reagent. These dimethoxyethane solutions were prepared by removing the ether under reduced pressure after combining 75 ml. of dimethoxyethane with 75 ml. of the organometallic solution.

The reactions carried out at −30° (runs 35 and 36) were run in a manner the same as runs at 0° (runs 27 and 21) except for the temperature difference.

The yields of all the reactions were calculated from the amount of unreacted starting material by estimating the amount present

from the intensity of the carbonyl absorption at 1670–1715 cm.$^{-1}$ in the infrared.

In those runs in which phenylorganometallic reagents were employed, the products were chromatographed on neutral alumina, unreacted bromobenzene and biphenyl being eluted with pentane, and product being eluted with ethyl acetate.

Starting ketone was removed with Girard reagent by a method previously recorded[15] in those runs whose product showed carbonyl absorption. In those runs which involved 2,3-diphenyl-3-hydroxy-2-butanone as starting material, this method failed to remove starting material. These products were reduced with excess lithium aluminum hydride, and careful chromatography of the product on neutral alumina allowed separation of the secondary and tertiary alcohols. The latter was eluted with a 25:75% mixture of ethyl acetate–ether. Control runs established the reliability of this method of separation.

Reactions Leading to 2,3-Diphenyl-3-methoxy-2-butanols.— These reactions were conducted identically to those leading to the 2,3-diphenyl-2,3-butanediols except that the appropriate methoxy ketones were substituted for the hydroxy ketones. After the carbonyl compound was added to the organometallic, the reaction mixture was stirred for 1.5 hr. The yields of these reactions were estimated from the intensity of the carbonyl absorption of the products at 1715 cm.$^{-1}$ for reactions involving (±)-3-methoxy-3-phenyl-2-butanone and at 1680 cm.$^{-1}$ for reactions with (±)-1,2-diphenyl-2-methoxy-1-propanone as starting material.

Analysis of Diastereomers.— The mixture of diastereomers produced when 2,3-diphenyl-2,3-butanediol was product was analyzed by the method developed earlier.[4] Results of comparable internal consistency were obtained in this as in the previous investigation.[4]

The mixtures of diastereomers of 2,3-diphenyl-3-methoxy-2-butanol produced were analyzed as follows. The *threo* isomer possessed infrared spectral bands at 1353, 1191, 1151 and 1059 cm.$^{-1}$ which were not present in the *erythro* isomer. The spectrum of the *erythro* isomer did not possess any bands not present in the *threo* isomer. Thus the 4 bands of the *threo* isomer were used in the analysis.

(15) D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **79**, 2872 (1957).

TABLE VI

INFRARED ANALYSIS^a OF PERCENTAGE DIASTEREOMERIC MIXTURES OF 2,3-DIPHENYL-3-METHOXY-2-BUTANOLS^b

Run	1353 cm.$^{-1}$ threo	1191 cm.$^{-1}$ threo	1151 cm.$^{-1}$ threo	1059 cm.$^{-1}$ threo	——Average—— threo	erythro
38	39	38	22	35	33	67
39	43	38	28	37	37	63
40	72	71	67	69	70	30
41	44	41	52	44	45	55
42	45	43	51	50	47	53
44	83	89	89	87	87	13
45	82	88	88	86	86	14
46	89	95	93	93	93	7
47	91	96	97	95	95	5
48	90	95	95	90	93	7

^{a} A Perkin–Elmer model 21 recording spectrophotometer, sodium chloride prism, cell thickness 0.096 mm., was used. ^{b} Amount of *erythro* in mixture equals $100\% - \%$ *threo*.

The samples (oils) to be analyzed were heated as a film to 80° for 1 hour at 1 mm. to remove the last traces of solvent. The oils (1.000 g.) were dissolved in 15.00 g. of carbon tetrachloride. Standard solutions of the same concentration of pure *threo* and *erythro* isomers were prepared, as well as four synthetic mixtures (1:4, 1:2, 1:1, 2:1, 4:1). The absorption band at 1450 cm.$^{-1}$ for both *threo* and *erthro* isomers was used as an internal standard. Spectra of the known and unknown samples were taken and all spectra were normalized to an absorbance of 0.452 at 1450 cm.$^{-1}$. The corrected optical densities of the known mixtures at the 4 different wave lengths were plotted against the % composition. The compositions of the unknowns were then read from the graphs. An average of the values at the 4 different wave lengths was taken to be the correct value for the unknowns. The results are recorded in Tables VI, III and IV.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES 24, CALIF.]

Studies in Stereochemistry. XXXIII. Approaches to Models for 1,3-Asymmetric Induction[1]

By DONALD J. CRAM AND DONALD R. WILSON[2]

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Systems have been investigated that might serve as models for 1,3-asymmetric induction in the anionic polymerization of olefins. Measurement of the *erythro/threo* ratio in the production of III from I and II was conceived as a model for isotactic polymerization. The ratio of *threo/erythro*-VII in the addition of V to VI might serve as a model for syndiotactic polymerization. Addition of I to II failed because of intervention of an elimination reaction of I to give propene and the products of reactions of the 9-methyl-9-methylfluorenyl anion. Organometallic compound V failed to add to VI. Both diastereomers of VIII were prepared and their configurations determined. The ratio of diastereomers formed by addition of carbon dioxide and formaldehyde to V was measured and found to be independent of which diastereomeric bromide served as starting material for preparation of the Grignard reagent. The *erythro/threo* ratio of products varied from 1.27 to 1.12. This result is interpreted as reflecting the ratio of diastereomeric Grignard reagents initially formed rather than the relative energies of the transition states for the addition reactions. "Paper models" for stereospecific anionic ploymerization are discussed.

One of the more challenging stereochemical problems of current interest involves development of an understanding of why certain polymerization reactions produce configurationally ordered chains which contain asymmetric centers at regular intervals. Most of these polymerizations involve addition reactions to carbon–carbon double bonds to give asymmetric centers 1, 3 to one another. Mechanisms available for rationalization of the observed stereoregularity fall into three classes: (1) those which place a stereochemical memory at the very end of each growing chain in the form of asymmetric catalytic sites[3]; (2) those which invoke 1,3-asymmetric induction in the formation of each new asymmetric center[4]; (3) those which point to asymmetric induction and involve sites further down the chain than the last asymmetric center.[4a,5]

This paper reports the results of an attempt to find reactions which would allow an experimental evaluation of the magnitude of effects in 1,3-asymmetric induction. The reaction, I + II → III, was conceived as a possible model for isotactic, and V + VI → VII for syndiotactic, polymerization. These reactions were selected for two reasons. (1) Analogies for these addition reactions were available in the literature.[6] (2) The relative configurations of the diastereomers of III and VII could be determined through use of the

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