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ASYMMETRIC SYNTHESES WITH R-α-HYDROXYPROPIONALDEHYDE

TEMPERATURE DEPENDENCE OF THE DIASTEREOMERIC PRODUCT RATIO

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Abstract—In an effort to test the applicability of the semi-empirical model for asymmetric induction[1] to reactions of α-hydroxycarbonyl compounds, we monitored the diastereomeric ratio of diols obtained from the reactions of R-α-hydroxypropionaldehyde with LAH, MeLi and PhLi as a function of temperature and reagent concentration. In all these reactions the predominant diastereomer had the *RR*-configuration. However, whereas the diastereomeric product ratio of the first two reactions was enthalpy controlled, i.e. enthalpy favored the "correct" or predominant diastereomer, that of the reaction involving PhLi favored the "incorrect", or minor diastereomer. In this reaction the diastereomeric ratio was entropy controlled. The usefulness and limitations of this model are discussed.

The open chain model[1] and its variations,[2] which are used to predict product stereospecificity for asymmetric synthesis with carbonyl compounds bearing an asymmetric C atom directly bonded to the CO, suffer from occasional inconsistencies[3] with respect to the relative steric bulk of the groups attached to the α-carbon and the nature of nonbonded interactions controlling stereospecificity. Particularly the models apply poorly[4] when one of the groups attached to the asymmetric carbon is polar such as hydroxy or amino, and can coordinate strongly with the attacking reagent.

Karabatsos,[5] applying the Curtin–Hammett[6] principle proposed that in addition reactions to carbonyl compounds, the diastereomeric product ratio at a given temperature depends only on the free energy difference ($\Delta\Delta G^{\ddagger}_{AB}$) of the two diastereomeric transition states and not on the individual ground state energies of the various conformations of the reactants as assumed in the previous models.[1,2]

In order to predict the diastereomeric product ratio and since the structures of the transition states are not accessible experimentally, the following assumptions were made:(5) (a) The two transition states resemble the reactants; (b) The two transition states controlling product formation have the incoming group nearest the smallest group of the α-carbon; and (c) the product ratio reflects the magnitude of the carbonyl eclipsed interactions, M↔O and L↔O.

It was pointed out[5] that the predictions of the model are limited because: (a) The model neglects interactions other than the M↔O and L↔O; (b) the model cannot account for differences in the solvation of the two diastereomeric transition states; and (c) there is no good way to evaluate differences in relative nonbonded interactions as a function of the effective size of the incoming group. The model effectively applies to cases where $\Delta\Delta H^{\ddagger}_{AB}$ controls $\Delta\Delta G^{\ddagger}_{AB}$ and $\Delta\Delta S^{\ddagger}_{AB}$ is minimal. In cases where $\Delta\Delta S^{\ddagger}_{AB}$ is large any success that this, or any other model, may have would be fortuitous.

In the present paper we will discuss the applicability of the model to reactions of carbonyl compounds bearing a polar group (OH) on the asymmetric carbon *alpha* to the carbonyl as $\Delta\Delta S^{\ddagger}_{AB}$ values are expected to be significant.[5] We will concentrate on additions to *R*-α-hydroxypropionaldehyde and the effect that variation in temperature, reagent and concentration of reactants have on product stereospecificity.

RESULTS

Optically active *R*-α-hydroxypropionaldehyde prepared from L-threonine by the ninhydrin method,[7] was used in all experiments. Its structure and stereochemistry were confirmed by reduction with LAH to *D*-1,2-propanediol as well as by the NMR spectra of the monomeric aldehyde and its 2,4-dinitrophenylhydrazone. LAH, MeLi and PhLi were allowed to react with *R*-lactaldehyde at different temperatures and the diastereomeric product ratio and the absolute configuration of the diols were determined by polarimetry, NMR spectroscopy and total synthesis (Experimental).

The free energy differences between the two transition states leading to the products were calculated according to the Curtin–Hammett principle,[6] $\Delta\Delta G^{\ddagger}_{AB} = RT \ln (A/B)$. From these values the differences in enthalpy and entropy were determined by the use of known thermodynamic relationships.

Table 1 shows the ratio of the diastereomeric 1,2-propanediols-1-*d* produced by the reduction of *R*-lactaldehyde with LAD in the temperature range 35° to −42°.

The ratio and the absolute configuration of the diastereomeric 1,2-propanediols-1-*d*, were determined from the NMR of their *p*-NO_2-benzylidene derivatives **1** and **2**. The stereochemistry of the *RR*- and *RS*-1,2-propanediols-1-*d*, has been established by total synthesis from the *cis* and *trans*-1-bromopropenes.[8] To calculate the ratio of the diastereomeric products we prepared the *p*-nitrobenzylidene derivatives of 1,2-propanediols, **1**, **2** and **3**. The C-1 hydrogens of **3** appear as two doubles ($J_{gem} = 7.8$ Hz) at $\tau = 5.9$ for the hydrogens *cis* to the deuterium on C-2 and at $\tau = 6.5$ for the hydrogens *trans* to the deuterium.

Table 1. Effect of temperature on the reduction of and addition of organolithium compounds to R-α-hydroxypropionaldehyde[a] in ether

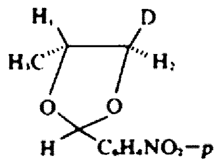
Temp. °C	Reagent	Products *RR*	–*RS*	Product[b] ratio	$-\Delta\Delta G^{*}$ cal/mole
	LAD[c]	1,2-propanediols-1-*d*			
35		56.1	43.9	1.27	146 ± 50
29		57.1	42.9	1.33	170 ± 38
0		58.4	41.6	1.40	182 ± 35
−21		59.0	41.0	1.44	182 ± 36
−42		60.0	40.0	1.50	185 ± 26
	MeLi[d]	2,3-butanediols			
35		60.6	39.4	1.53	259 ± 50
15		61.0	39.0	1.56	253 ± 48
−3		62.2	37.8	1.64	264 ± 45
−13		63.0	37.0	1.70	273 ± 40
−15		62.8	37.2	1.68	265 ± 40
−43		63.5	36.5	1.73	249 ± 39
−65		65.6	34.4	1.90	264 ± 37
	PhLi[d]	1-phenyl-1,2-propanediols			
35		73.0	27.0	2.70	605 ± 65
16		72.7	27.3	2.66	559 ± 60
0		72.0	28.0	2.57	510 ± 52
−13		71.9	28.1	2.55	481 ± 47
−30		70.0	30.0	2.33	403 ± 43
−60		68.0	32.0	2.12	316 ± 35

[a] The concentration of the aldehyde in all reactions was 0.25 molar.

[b] The values are the average of 3–4 experiments.

[c] Concentration 0.25 molar in final volume. Molar ratio of substrate: reagent was 1:1. Stoichiometry of the reaction for reduction and complexation with α-hydroxy requires 1:0.5.

[d] Concentration 0.52 molar in final volume. Molar ratio of substrate: reagent was 1:2.



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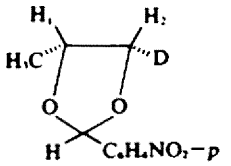

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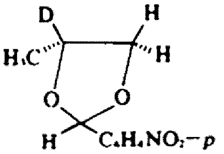


3

The important region of the NMR spectra of the mixture of 1 and 2 shows a doublet at $\tau = 6.4$ ($J = 7.5$ Hz) which has been assigned[7,8] to the H_1 *trans* to H_2 of 1 and a multiplet at $\tau = 5.7$ assigned to the H_1 *cis* to H_2 of 2 and the protons H_2 of 1 and 2. In 1 carbon-1 has the *R* configuration and the diol is the *RR*; in 2 carbon-1 has the *S* configuration and the diol is the *RS*.

If the absorption at $\tau = 6.4$, which belongs to the H_1 of *RR* is given the value x, and the absorption at $\tau = 5.7$, which belongs to the sum of H_1 of *RS* plus H_2 of *RR* and H_2 of *RS* is given the value y, and since $H_1RR = H_2RR = x$, then the sum of vicinal protons in *RR* is 2x and that in *RS* is y-x. According to this, the ratio calculated from the experimental data was 56% *RR* and 44% *RS*. From Table 1 it can be seen that at all temperatures the predominant diastereomer is the *R*-1,2-propanediol-1-d_1, whose percentage increases with decrease of temperature. The calculated values of enthalpy and entropy differences ($\Delta\Delta H^{*} = -280$ cal/mole and $\Delta\Delta S^{*} = +0.4$ e.u.) indicate that the transition state leading to the *RR*-propanediol is more stable than the one leading to the *RS*-diastereomer primarily because enthalpy favors it by 280 cal/mole entropy playing a minor role.

The reaction of MeLi with *R*-lactaldehyde in the temperature range 35° to −65° yielded a mixture of diastereomeric 2,3-butanediols. The diastereomers *RR* and *meso*-2,3-butanediols were separated by gas chromatography on a FFAP 20%, Chromosorb W column. Their stereochemistry was established by NMR spectroscopy and polarimetry. The specific rotation of the one isomer in water was $[\alpha]^{25}_{589\,m\mu} = -10.8$ a value which agrees with the one reported in the literature[9] for the *RR*-2,3-butanediol. The other diastereomer was the *RS* or *meso*-diol. The NMR spectra of each diol and their acetonides are type $X_3AA'X'_3$ and were analyzed with empirical methods.[10] The values of the vicinal coupling constants of the *RR* and *RS*-2,3-butanediols depend strongly on the polarity of the solvent. Polar solvents increase the vicinal coupling constants of the *meso*-diol and have the opposite effect on the vicinal coupling constants of the *RR*-diol. Thus, J_{H_1}–J_{H_2} of the *meso*-diol in deuterochloroform and dimethylsulfoxide-d_6 are 3.13 Hz and 5.4 Hz respectively. The values of $J_{H_1-H_2}$ of the *RR*-diol in deuterochloroform and dimethylsulfoxide-d_6 are 6.9 Hz and 5.46 Hz respectively. This is probably due to the change of populations of the *trans* and *gauche* rotamers of the diastereomeric diols.[11] Table 1 shows the ratio of *RR*/*meso* diastereomers. The predominant diastereomer in all temperatures is the (−)*RR*-2,3-butanediol. The ratio *RR*/*meso* at 35° is 1.5 and increases as the temperature decreases. Here again the reaction is enthalpy controlled ($\Delta\Delta G^{*} = -260$ cal/mole, $\Delta\Delta H^{*} = -260$ cal/mole). Use of methyl magnesium chloride as a nucleophile (in a ratio *R*-lactaldehyde/nucleophile 1:2 in ether) increased slightly the stereospecificity of the reaction (*RR*/*meso* = 1.85 at 0°).

Reaction of phenyllithium with *R*-lactaldehyde gave a mixture of diastereomeric 1-phenyl-1,2-propanediols whose structure and absolute configuration were confirmed by NMR, polarimetry and total synthesis.

The NMR of a mixture of diastereomers in chloroform showed two doublets at $\tau = 5.74$ ($J = 7.6$ Hz) and $\tau = 5.36$ ($J = 3.6$ Hz) which are assigned to the vicinal protons of the *RR* and *RS* diastereomers respectively. The assignment is based on comparison of their shifts and coupling constants with those of authentic diastereomeric diols as outlined below. (±) *threo*-1-Phenylpropanediol was obtained by *cis* hydroxylation of (±) *trans*-1-phenyl-1-propene. The doublet of the vicinal protons absorbed at $\tau = 5.65$ ($J = 7.2$ Hz) in deuterochloroform. (±) *erythro*-1-Phenylpropanediol (53%) was obtained with (±) *threo*-1-phenylpropanediol (47%) from the acid hydrolysis of (±) *trans*-1-phenylepoxypropane. The doublet of the vicinal protons of the *erythro*-diol absorbed at $\tau = 5.25$ ($J = 3.4$ Hz) in deuterochloroform. The values of the coupling constants are in agreement with those reported in the literature.[12] The coupling constants J_{H_1}–J_{H_2} are affected strongly by the dielectric constant of the solvent. For example, J_{H_1}–J_{H_2} of the *RR*-diol in carbon tetrachloride and dimethylsulfoxide-d_6 are 7.8 Hz and 6.6 Hz respectively and $J_{H_1H_2}$ of the *RS*-diol in the same solvents are 3.8 Hz and 4.8 Hz respectively. Integration of the areas at $\tau = 5.74$ and $\tau = 5.36$ gives a ratio 73/27 of

RR/*RS* diastereomers (reaction temperature 35°). This ratio agrees with the results obtained by integration of the peaks of diols estimated by gas chromatography through a FFAP 20%, Chromosorb W Column. Purification of the mixture of diols by distillation or gas chromatography did not affect this ratio.

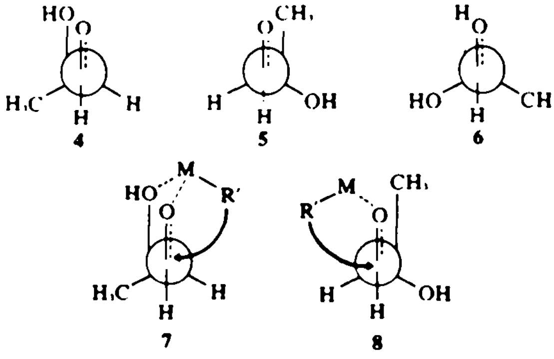
The major product obtained from the reaction was (−) *threo*-1-phenylpropanediol (*RR* configuration); and the minor product was (+) *erythro*-diol of *RS* configuration. These products are identical to the diols obtained by alkaline and acid hydrolysis of (+) *trans*-1-phenylepoxypropane of *RR* configuration. (+) *trans*-1-Phenylepoxypropane was obtained from *L*-ephedrine (*RS* configuration) according to known methods.[11] Alkaline hydrolysis with potassium carbonate of the *RR*-phenylepoxypropane gave by Walden inversion at C-1 100% (+) *RS*-1-phenyl-propanediol.[11b] Acid hydrolysis with sulfuric acid of the epoxypropane yielded a mixture of 62% (+) *erythro* and 38% (−) *threo*-1-phenylpropanediol.[11] The two diastereomers are formed from opening of the protonated (+) - *trans* - 1 - phenylepoxy - propane (R_1R_2) to the carbonium ion $C_6H_5-^{+}CH-CH(OH)CH_3$ and capture of it by water to give (+) *erythro* diastereomer R_1S_2 (by inversion at C-1), and (−) *threo* R_1R_2 (by retention of configuration at C-1).

The effect of temperature on the ratio of diastereomeric diols as shown in Table 1 is quite interesting. The diastereomer *RS* is favored as a result of entropy ($\Delta\Delta S^{\neq} = -2.8$ e.u.) rather than enthalpy, which favors the *RR* diastereomer ($\Delta\Delta H^{\neq} = +340$ cal/mole).

In the reduction of *R*-lactaldehyde with lithium aluminum deuteride and the addition of methyl or phenyllithium to *R*-lactaldehyde the ratio of substrate to reagent was 1:2 when the reagent was MeLi or PhLi and 1:1 when the reagent was LAD. Change of the concentration of the lactaldehyde from 0.35 to 0.05 molar (final volume) had no effect on the ratio of the diastereomeric diols for a given temperature.

DISCUSSION

The stable conformations of aldehydes about the sp^2–sp^3 C–C single bonds are those where a single bond eclipses the double bond of the CO group.[14] In propionaldehyde, the conformer with the Me eclipsing the CO is favored over the conformer with the hydrogen eclipsing, by about 800 cal/mole. In α-methoxyacetaldehyde, the energetically favored (1200 cal/mole in polar solvents) conformer is the one where the OMe group eclipses the CO. Assuming that the conformations of α-*R*-hydroxypropionaldehyde (*R*-lactaldehyde) parallel those of α-methoxyacetaldehyde we expect rotamer **4** to be more stable than **5**, and **5** to be more stable than **6** (Scheme 1).



Scheme 1.

According to the semiempirical model[5] the two low energy diastereomeric transition states which control product stereospecificity have the incoming reagent nearest the smallest group of the α-C atom. If little bond breaking and making occurs in the diastereomeric transition states then **7** and **8** would be the simplified representations of the two low energy transition states. These transition states should complex extensively with the reagent at both oxygens and differ significantly in dipole moment and extent of solvation. Of the two, **7** ought to be more stable not only because of the stability impartet by the pseudo-ring formation but also because the OH↔O interaction should be favored over the Me↔O interaction.

Based on the above reasoning the predicted major diastereomer from the reduction of *R*-lactaldehyde should have the *RR*-configuration, deriving from transition state **7** and the minor diastereomer the *RS*-configuration deriving from transition state **8**.

Several authors[2a,4,15-17] have studied the stereospecificity of addition reactions to carbonyl compounds which bear an heteroatom (OH, NH_2) substituent on the asymmetric carbon attached to the CO and tried to interpret their results in terms of the cyclic,[2a] dipolar[2b] or other variations of the open chain model. However, for a number of reactions of organolithium reagents with α-hydroxy carbonyl compounds the predicted by the cyclic model predominant diastereomer did not agree with the experimental data. For example, Stoker *et al.*[4] found that the diastereomeric product ratio of the addition of phenyllithium to 3 - hydroxy - 3 - phenyl - 2 - butanone, 87% + *threo* (*SR* + *RS*) and 13% + *erythro* (*SS* + *RR*) was in agreement with the prediction of the cyclic model. However, for the addition of MeLi to 2-hydroxy-1,2-diphenylpropanone the experimental diastereomeric ratio *threo*/*erythro* was less than unity (9/91), i.e. reverse from the one predicted by the cyclic model. Similar results were obtained by Cram *et al.*,[2] who found that whereas the addition of PhLi to 3 - methoxy - 3 - phenyl - 2 - butanone yielded predominantly the *threo* isomer (90%) as predicted by the cyclic model, the addition of MeLi to 1,2 - diphenyl - 2 - methoxy - propanone gave predominantly the *erythro* isomer. It is conceivable that these anomalies are due to differences in solvation of the two transition states **7** and **8** and significant contribution of $\Delta\Delta S^{\neq}_{AB}$ to $\Delta\Delta G^{\neq}_{AB}$.

These is no extensive study on the influence of solvent on the stereospecificity of the reactions of assymetric synthesis with carbonyl compounds. However, there are indications that the stereospecificity of these reactions is increased in polar solvents. The difference in free energy of activation for the addition of MeLi to methylbenzoin became more negative in ether than in pentane ($\Delta\Delta G^{\neq} = -1.3$ in ether, $\Delta\Delta G^{\neq} = -0.75$ in pentane). The diastereomeric product ratio of the addition of PhLi to phenylacetoin is smaller in pentane (1:5 *meso*/*dl*) than in ether (1:10, *meso*/*dl*).[4a] Similar results were obtained in the addition of MeLi to 3-phenyl-2-butanone-1,1,1,3-3-d_4 in ether or pentane ($\Delta\Delta G^{\neq} = -0.97$ in ether, $\Delta\Delta G^{\neq} = -0.7$ in pentane), and the addition of MeLi to 4 - methyl - 3 - phenyl - 2 - pentanone - 1,1,1,3 - d_4 ($\Delta\Delta G^{\neq} = -1.05$ in ether, $\Delta\Delta G^{\neq} = -0.44$ in pentane[18]). The decrease in stereospecificity may arise either from differences in the structure of MeLi in the different solvents or from differences in stability of the two important transition states, with the polar solvent[19] stabilizing the more polar transition state **7**. The structure and degree of polymerization of the organometallic reagents[20] and metal hydrides[21] in the different solvents is by far not elucidated. Neither the mechanism nor the molecularity of the addition reactions to carbonyl compounds has been established unambiguously.[22,23]

Temperature effects

It has been stated[4] that any predictions for the stereospecificity of reactions of asymmetric synthesis based on the model is valid only when the differences in the free energies of activation are controlled by enthalpy. In the present work we studied the effect of temperature on the stereospecificity of the reactions of *R*-lactaldehyde with metal hydrides, MeLi and PhLi in order to examine the factors which control the activation parameters.

In the reduction of *R*-lactaldehyde with LAD between 35° and −40° it can be seen (Table 1) that the decrease in temperature favors the formation of the predominant diastereomer. The contribution of the entropy differences to the free energy differences is very small and the predictions of the model are valid.

The same effect of temperature was observed in the reaction of MeLi to *R*-lactaldehyde between 35° and −60°. The reaction is enthalpy controlled.

In the case of the addition reaction of PhLi to *R*-lactaldehyde the decrease in temperature favors the "wrong" diastereomer. Linear Arrhenius plots (Fig. 1) were obtained and both, differences in enthalpy and entropy were found to contribute to the differences of the free energy of activation. Unfortunately, there are not enough published data on the effect of temperature on asymmetric synthesis. In Table 2 we include five categories of reactions of aldehydes or ketones with organometallic reagents where the effect of temperature was studied: (1) reactions where R is branched (isopropyl, t-butyl, neopentyl), (entries **2–6**) (2) reactions

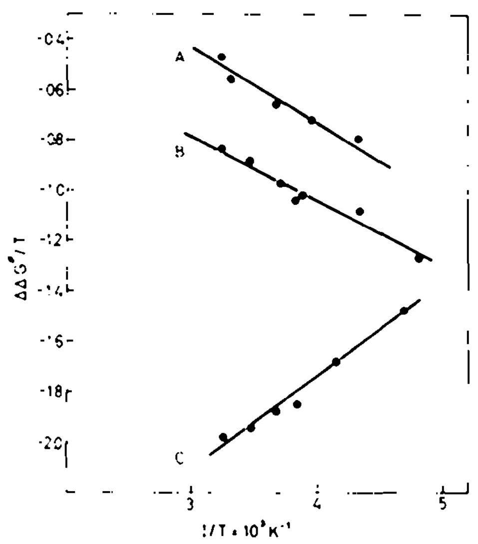


Fig. 1. Arrhenius plots of reactions with *R*-α-hydroxypropionaldehyde (A) Reduction with lithium aluminum deuteride, $\Delta\Delta H^{\neq} = -280 \pm 30$ cal/mol, $\Delta\Delta S^{\neq} = +0.4$ e.u. (B) Addition of methyl lithium, $\Delta\Delta H^{\neq} = -260 \pm 30$ cal/mol, $\Delta\Delta S^{\neq} = +0.003$ e.u. (C) Addition of phenyl lithium, $\Delta\Delta H^{\neq} = +340 \pm 40$ cal/mol, $\Delta\Delta S^{\neq} = -2.8$ e.u.

Table 2. Activation parameters in the asymmetric addition reactions to ketone $R_1R_2CH{-}COR$ in ether at 35°C

No.	Ketone R_1	R_2	R	Reagent	$-\Delta\Delta G^{\neq}$ cal/mol	$-\Delta\Delta S^{\neq}$ cal/mol	$-\Delta\Delta S^{\neq}$ e.u.
1	C_6H_5	CH_3	CH_3[a]	$LiAlH_4$	600	900	−0.9
2	C_6H_5	CH_3	$CH(CH_3)_2$[b]	$LiAlH_4$	910	200	2.4
3	C_6H_5	CH_3	$C(CH_3)_3$[b]	$LiAlH_4$	2100	2700	−2.0
4	C_6H_5	CH_3	$CH_2C(CH_3)_3$[c]	$LiAlH_4$	150	−300	1.4
5	C_6H_5	CH_3	$CH_2C(CH_3)_3$[c]	C_6H_5Li	810	640	0.6
6	C_6H_5	CH_3	$CH_2C_6H_5$[d]	$C_6H_5CH_2MgI$	740	680	0.2
7	C_6H_5	C_2H_5	H[e]	$LiAlD_4$	200	400	−0.6
8	C_6H_5	$CH(CH_3)_2$	H[d]	$LiAlD_4$	520	500	0.1
9	C_6H_5	$CH(CH_3)_2$	CH_3[d]	MeMgI[i]	140	400	−0.9
10	C_2H_5	CH_3	CH_3[a]	$LiAlH_4$	−40	150	−0.6
11	$(CH_3)_3C$	CH_3	CH_3[c]	$LiAlH_4$	100	−800	3.0
12	$(CH_3)_3C$	CH_3	CH_3[c]	MeMgCl[j]	700	−2700	10.0
13	CH_3	OCH_3	CH_3[f]	MeLi	520	40	1.8
14	CH_3	OH	H[g]	$LiAlD_4$	150	280	−0.4
15	CH_3	OH	H[g]	MeLi	259	260	0.00
16	CH_3	OH	H[g]	C_6H_5Li	600	−340	2.8
17	$(C_6H_5)(Me)CHCH_2COMe$[h]			C_6H_5MgBr	490	590	−0.3
18	$C_6H_5(Me)CHCH_2COC_6H_5$[h]			MeMgBr	−200	50	−0.5

[a] Y. Gault and H. Felkin, *Bull. Soc. Chim. Fr.* 1342 (1960). M. Cherest, H. Felkin and N. Prudent, *Tet. Letters* 2199 (1968).

[b] G. J. Karabatsos, C. Zioudrou and I. Moustakali, *Tet. Letters* 5289 (1972); C. Zioudrou *et al.*, unpublished results.

[c] C. Zioudrou, P. Chrysochou, G. J. Karabatsos, D. H. Herlem and R. P. Nipe, *Tet. Letters* 5293 (1972).

[d] T. A. Althuis, Ph.D. Thesis, Michigan State University (1968).

[e] L. Valles, Master's Thesis, Michigen State University (1970).

[f] Y. Ara, Ph.D. Thesis, Michigen State University (1971).

[g] Present work.

[h] T. J. Leitereg and D. J. Cram, *J. Am. Chem. Soc.* **90**, 4011 (1968) (1,3-asymmetric induction).

[i] Temperature 25°.

[j] Solvent THF and temp. 66°.

where the medium size group of the asymmetric α-carbon is alkyl other than Me, (entries 7–9) (3) reactions where the large size group (Ph) is replaced by an alkyl group (entries 10–12), (4) reactions where one group on the asymmetric α-carbon is oxygen, and (5) 1,3-asymmetric synthesis reactions (entries 17, 18).

In most cases $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ contribute to the differences of the free energy of activation. In entries 1, 3, 7, 9, 14, 17 enthalpy is the major activation parameter which controls the reactions. In entries 4, 10, 11, 12, 16 the values of $\Delta\Delta G^{\neq}$ and $\Delta\Delta H^{\neq}$ have opposite signs, $\Delta\Delta G^{\neq}_{AB}$ goes through zero at a given temperature and the predictions of the model are incorrect on one side of the temperature scale.

The effect of temperature on product stereospecificity can be extremely complex since changes in temperature can alter the dielectric constant of the solvents, the degree of association and structure of the reagent and finally may result in change of mechanism.

In conclusion from the data presented we would like to restate: (1) In entropy controlled cases the predictions of any model may be incorrect, and (2) the effect of temperature, solvent, structure of nucleophile and concentration on the diastereomeric product ratio support the assumption that the products derive from two different transition states 7 and 8.

EXPERIMENTAL

Li shot[24] containing 2–5% metallic Na[25] was used for the preparation of MeLi or PhLi in ether or pentane. The molarity of the ethereal solns of the organolithiums was determined according to Jones and Gilman.[26] LAD (99%) was purchased from Merck Sharp Dohme and LAH and $NaBH_4$ from Fluka.

The NMR spectra were recorded with an A-60-A Varian spectrometer. A thermal conductivity Varian aerograph Model 90-P was used for the purification and separation of diastereomers. The specific rotations were measured with a Perkin Elmer 141C Photoelectric polarimeter. All reactions were run under constant temp using a circulating bath (Ultra Kryostat K-75 DW, Lauda) and the temps were maintained constant between ± 1 degree. Temps were measured using calibrated iron-constantan thermocouples. The errors in $\Delta\Delta G^{\neq}$ values were calculated on the basis of the errors in the diastereomeric product ratio.

R-α-Hydroxypropionaldehyde was prepared by the ninhydrin method from *L*-threonine[7a,b] with some modifications. Pure liquid monomeric *R*-lactaldehyde was obtained by fractional distillation (b.p. 38° at 5 mm Hg). The receiver pot of the distillation apparatus was cooled with dry ice-propanol soln in order to maintain the lactaldehyde as a monomer. The NMR spectrum in DMSO of the monomer shows a Me doublet at $\tau = 8.67$ (J = 7.25 Hz); a quintet resulting from two superimposed quartets corresponding to the α-proton and its coupling with the Me (J = 7.25 Hz) and with the OH (J = 5.5 Hz), a doublet at $\tau = 4.45$ corresponding to the OH, split by the α-proton with J = 5.5 Hz; and finally a doublet belonging to the aldehydic proton at $\tau =$ 0.2 ppm and J – 1 Hz. The spectrum changes with time due to the dimerization of the aldehyde to the corresponding 1,4-dioxane derivative. The process of dimerization can be followed by the disappearance of the aldehydic proton. The kinetics of the reaction are complex and will be reported elsewhere.

The specific rotation of *R*-lactaldehyde depends on the degree of dimerization. Freshly prepared monomer has a specific rotation $[\alpha]^{25}_{589\,nm} = +5.4$ (*c*, 5.7 in H_2O); after 150 minutes the specific rotation of the soln is $[\alpha]^{25}_{589\,nm} = -3.3$. Specific rotation in benzene was found to be $[\alpha]^{25}_{589\,nm} = +5.8$ (*c*, 11 in benzene); reported in benzene $[\alpha]^{25}_{D} = +2.65$[27].

The NMR spectrum of 2,4-dinitrophenylhydrazone of *R*-lactaldehyde (m.p. 155–158°; reported 156–157°[7a]) shows all the characteristic protons of the monomeric aldehyde hydrazone. Reduction of *R*-lactaldehyde with LAH yielded *D*-1,2-propanediol $[\alpha]^{25}_{589\,nm} = -21.9$; reported $[\alpha]^{25}_{D} = -21.3$.[28] *D*-Propanediol and its *p*-nitrobenzylidene derivative were also characterized by their NMR spectra.

D-1,2-*Propanediol*-1-d was prepared by reduction of *R*-lactaldehyde (20 mmole) with LAD (20 mmole) in ether and purified by VPC on Apiezon L 20%, Chromosorb W column at 125°.

D-1,2-*Propanediol*-2-d was prepared and purified similarly by reduction of hydroxyacetone with LAD.

p-*Nitrobenzylidene derivatives of deuterated* 1,2-*propanediol* were prepared as described by Zagalak *et al.*[7b,29]

2,3-*Butanediols* were prepared by addition of *R*-lactaldehyde (40 mmole) to a soln of MeLi (82 mmole) in ether. The diastereomeric diols were separated by VPC through an FFAP 20%, Chromosorb W column at 100° and 40 psi. Ratio of retention time *RS*/*RR* was 1.2. The diastereomeric product ratio was determined by VPC using as standard (±) *threo*(*RR* + *SS*) and *erythro*-(*meso*) 2,3-butanediols. Specific rotation $[\alpha]^{22}_{589\,nm} = 11.3$; reported $[\alpha]^{22}_{D} = -11$.[9] Reverse additions of reagents did not affect the diastereomeric product ratio.

1-*Phenyl*-1,2-*propanediols* were prepared by addition of *R*-lactaldehyde (40 mmole) to an etherial soln of PhLi (82 mmole). The mixture of 1 - phenyl - 1,2 - propanediols was purified by distillation (90–100° at 0.5 mm Hg). The structure and diastereomeric product ratio were determined by NMR and VPC. The ratio of retention time was *RS*/*RR* = 1.08 on a FFAP 20%, Chromosorb W at 180° and 60 psi.

The specific rotation of the (−)*RR* diol was $[\alpha]^{22}_{589\,nm} = -61.5$ (c, 4.3 in $CHCl_3$) and $[\alpha]^{22}_{589\,nm} = -49$ (c, 2.5 ethanol), that of the (+) RS diol was $[\alpha]^{22}_{589\,nm} = +17.2$ (c, 4.2 in ethanol) and $[\alpha]^{22}_{589\,nm} = +33$ (c, 3.2 in $CHCl_3$). Reported[13a] (−)*RR* = $[\alpha]^{22}_{D} = -60.6$ in $CHCl_3$ and (+)*RS* $[\alpha]^{22}_{D} = +16$ in ethanol.[13b]

Authentic-1-*phenylpropanediols*. (±)*threo* - 1 - Phenylpropanediol was obtained (100% yield) from the *cis* hydroxylation with aqueous potassium permanganate of *trans* - 1 - phenylpropene (Fluka) according to known methods.[30] (±)*erythro* - 1 - Phenylpropanediol was obtained (52.5% yield) together with (±) - *threo* - 1 - phenylpropanediol (47.5% yield) by acid hydrolysis with perchloric acid of (±) - *trans* - phenylepoxypropane.[13,31]

(±) - trans - 1 - *Phenylepoxypropane* was prepared from *trans* - 1 - phenylpropene by oxidation with perbenzoic acid according to known methods.[30] The vicinal *trans* protons appear as a doublet at $\tau = 6.64$ and J = 2 Hz.[12]

(+) - erythro - 1 - *Phenylpropanediol* (R_2S_1 configuration, C_1 bears the phenyl group) was obtained by alkaline hydrolysis of (+) - *trans* - 1 - phenylepoxypropane R_2R_1 configuration. The last was prepared from (−)-ephedrine (R_1S_2) according to known methods.[11] Its NMR spectrum was identical with that of (±) - *trans* - 1 - phenyl - epoxypropane and its specific rotation was $[\alpha]^{25}_{589\,nm} = +41.7$ (c, 2 in $CHCl_3$); reported $[\alpha]^{20}_{D} = +48.2$ in $CHCl_3$. The specific rotation of the (+)-erythro-diol was $[\alpha]^{22}_{589\,nm} = +17.2$ (*c*, 4 in ethanol); reported $[\alpha]^{25}_{D} = +16$ in EtOH.[13]

(−) - threo - 1 - *Phenylpropanediol* (R_1R_2 configuration was obtained (38% yield) together with (+) - *erythro* - diol (62% yield) from acid hydrolysis with sulfuric acid of the (+) - *trans* - 1 - phenylepoxypropane.[11] Specific rotation $[\alpha]^{22}_{589\,nm} = -61.5$ (c, 4.3 in $CHCl_3$); reported $[\alpha]^{25}_{D} = -60.6$ in $CHCl_3$.

By-products in the reaction of α - R - hydroxypropionaldehyde with methyl or phenyllithium. In the addition reactions of MeLi or PhLi to *R*-lactaldehyde we found that part of the lactaldehyde isomerized to hydroxyacetone identified by NMR analysis as the addition products 2 - methyl - 1,2 - propanediol and 2 - phenyl - 1,2 - propanediol respectively.

The presence of hydroxyacetone in *R*-lactaldehyde used in the experiments was excluded by NMR analysis. Hydroxyacetone absorbs at $\tau = 8.2$ (singlet for the Me protons) and at $\tau = 6.47$ (broad singlet for the methylene protons). The amount of 2-methyl or 2-phenyl-1,2-propanediols formed, i.e. per cent of hydroxyacetone, depended on the temp of the reactions. For example, in the reaction of MeLi with *R*-lactaldehyde at 35° and -65°, 30% and 5% of 2 - methyl - 1,2 - propanediol respectively were determined by integration of the absorptions at $\tau = 8.75$ (singlet for *gem*-Me protons) and $\tau = 6.56$ (singlet for methylene protons) of the 2 - methyl - 1,2 - propanediol and integration of the absorptions at $\tau = 8.84$ (doublet of Me protons) and $\tau = 6.3$ (multiplet of vicinal protons) of the 2,3-butanediols. 2 - Phenyl - 1,2 - propanediol in the product mixture was determined by integration of the absorptions at $\tau = 8.6$ (singlet of Me protons) and $\tau = 6.45$ (broad split singlet of methylene protons) of 2 - phenyl - 1,2 - propanediol and the absorptions at $\tau = 9.09$ (doublets of Me protons) and doublets at $\tau = 5.35$ and $\tau = 5.74$ of the vicinal protons of the 1 - phenyl - 1,2 - propanediols. Aldo-keto isomerization α-hydroxyaldehydes under a variety of conditions has been reported.[33]

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REFERENCES

[1] D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.* **74**, 5828 (1952).

[2a] D. J. Cram and K. R. Kopecky, *Ibid.* **81**, 2748 (1959); D. J. Cram and D. R. Wilson, *Ibid.* 1245 (1963); refer to the cyclic model. [b] J. W. Cornforth, R. H. Cornforth and K. K. Mathew, *J. Chem. Soc.* 112 (1959); refer to the dipolar model.

[3a] Y. Gault and H. Felkin, *Bull. Soc. Chim. Fr.* 1342 (1960). [b] D. J. Cram, F. A. Abd Elhafez and H. Weingartner, *J. Am. Chem. Soc.* **75**, 2293 (1953); D. J. Cram and F. A. Abd Elhafez, *Ibid.* **76**, 22 (1954); D. J. Cram and J. Allinger, *Ibid.* **76**, 4516 (1954); D. J. Cram and J. D. Knight, *Ibid.* **74**, 5835 (1952).

[4a] J. H. Stocker, P. Sidisunthron, B. M. Benjamin and C. J. Collins, *Ibid.* **82**, 3913 (1960). [b] J. H. Stocker, *J. Org. Chem.* **29**, 3593 (1964). [c] B. M. Benjamin, H. J. Schaeffer and C. J. Collins, *J. Am. Chem. Soc.* **79**, 6160 (1957). [d] S. Yamada, K. Koga, *Tetrahedron Letters* 1711 (1967).

[5] G. J. Karabatsos, *J. Am. Chem. Soc.* **89**, 1367 (1967).

[6] D. Y. Curtin, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **15**, 111 (1954).

[7a] E. Huff and H. Rudney, *J. Biol. Chem.* **234**, 1060 (1959). [b] B. Zagalak, P. A. Frey, G. J. Karabatsos and R. H. Abeles, *Ibid.* **241**, 3028 (1966).

[8] G. J. Karabatsos, J. S. Fleming, N. Hsi and R. H. Abeles, *J. Am. Chem. Soc.* **88**, 849 (1966).

[9] R. E. Reeves, *Ibid.* **69**, 1836 (1947).

[10] A. A. Bothner-By and C. Naar-Colin, *Ibid.* **84**, 743 (1962); [b] F. A. L. Anet, *Ibid.* **84**, 747 (1962).

[11a] D. A. Dawson and W. F. Reynolds, *Can. J. Chem.* **49**, 3438 (1971). [b] H. S. Gutowsky, G. G. Belford and P. E. McMahon, *J. Chem. Phys.* **36**, 3353 (1962).

[12] G. H. Schmid, *Can. J. Chem.* **46**, 3415 (1968).

[13a] C. M. Foltz and B. Witkop, *J. Am. Chem. Soc.* **79**, 201 (1957). [b] F. Fisher, *Chem. Ber.* **94**, 893 (1961).

[14] G. J. Karabatsos and D. J. Fenoglio, *Topics in stereochemistry* **5**, 167 (1970).

[15] D. Y. Curtin, E. E. Harris and E. K. Meislich, *J. Am. Chem. Soc.* **74**, 2901 (1952).

[16] For a summation of results see: D. J. Morrison and H. S. Mosher, *Asymmetric Reactions*, pp. 84–133. Prentice Hall, New Jersey (1971).

[17] D. R. Boyd and M. A. McKervey, *Quart. Rev.* **22**, 95 (1968).

[18] G. J. Karabatsos and T. H. Althuis, *Tetrahedron Letters* 4911 (1967).

[19] G. J. Karabatsos and D. J. Fenoglio, *J. Am. Chem. Soc.* **91**, 3577 (1969).

[20] P. West and R. Waack, *Ibid.* **89**, 4395 (1967).

[21] H. O. House, *Modern Synthetic Reactions*. Benjamin N.Y. (1965).

[22] T. L. Brown, *Adv. Organometal. Chem.* 3, 365 (1965); E. C. Ashby and J. T. Laemmle, *Chem. Rev.* **75**, 521 (1975); S. G. Smith, L. F. Charbonneau, D. P. Novak and T. L. Brown, *J. Am. Chem. Soc.* **94**, 705 (1972).

[23] B. Rickborn, M. T. Wuesthoff, *Ibid.* **92**, 6894 (1970).

[24] L. R. Worden and A. W. Burgstahler, *J. Chem. Education* **45**, 425 (1968).

[25] P. D. Bartlett and E. B. Lefferts, *J. Am. Chem. Soc.* **77**, 2804 (1955).

[26] R. G. Jones and H. Gilman, *Org. Reactions* **6**, 339 (1951).

[27] R. Dowarjak and H. Zellner, *Monatshefte für Chemie* **80**, 406 (1949).

[28] E. Baer, H. O. L. Fischer, *J. Am. Chem. Soc.* **70**, 609 (1948).

[29] L. F. Fieser, M. Fields and S. Lieberman, *J. Biol. Chem.* **156**, 191 (1944).

[30] *Org. Syntheses Coll.*, Vol. I, 413 (1941); D. Swern, *J. Am. Chem. Soc.* **70**, 1235 (1948).

[31] M. Swoboda and Y. Sicher, *Coll. Czech. Chem. Comm.* **20**, 1452 (1955).

[32] G. G. Lyle and L. K. Keefer, *J. Org. Chem.* **31**, 3921 (1966); J. Lehn and J. Riehl, *Mol. Phys.* **8**, 33 (1964).

[33] H. O. L. Fischer, C. Taube and E. Baer, *Ber. Dtsch. Chem. Ges.* **60**, 479 (1927); D. W. Griffiths and C. D. Gutsche, *J. Am. Chem. Soc.* 93, 4788 (1971).