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ASYMMETRIC INDUCTION IV. DEPENDENCE OF SOME DIASTEREOMERIC PRODUCT RATIOS ON $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$

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In the course of our investigations on the usefulness and validity of our model of asymmetric induction[1] we have obtained several results that cogently underline the dangers of placing too much faith on any model of asymmetric induction. We hope that the presentation of these results and the comments that follow will prove to be generally useful.

In Table I we have summarized the diastereomeric product ratios and $\Delta\Delta G^{\ddagger}$ values obtained from several additions to carbonyl compounds. We will discuss these data in terms of each of the three carbonyl systems listed in the Table.

1. The reaction of 2-phenylpropionaldehyde with neopentyllithium in ether at -35° gave the expected diastereomeric alcohols, A and B, in a ratio of 23/77, or a $\Delta\Delta G^{\ddagger}$ value of .58 kcal/mole. This value is consonant with the predicted [1] value of about .6 kcal/mole. The complementary reaction, i.e., the reduction of 2-phenyl-4,4-dimethyl-3-hexanone with lithium aluminum hydride, gave the data listed in entries 1-6 in Table I. At 35°, although the major diastereomer is the predicted A, $\Delta\Delta G^{\ddagger}$ is appreciably smaller than the expected value (.15 vs. .6 kcal/mole). More significantly, as the reaction temperature decreases, so does the ratio A/B. Indeed, below -60°, B, the "wrong" diastereomer, predominates. From the data, a $\Delta\Delta H^{\ddagger}_{AB}$ ($\Delta H^{\ddagger}_{A}$ - $\Delta H^{\ddagger}_{B}$) value of ca +.30

Table I

DIASTEREOMERIC PRODUCT RATIOS (A/B) AND $\Delta\Delta G^{\ddagger}_{AB}$ VALUES FROM ADDITIONS TO SOME CARBONYL COMPOUNDS.

No	Substrate	Nucleophile	Solvent	Temp., °C	A/B[a]	$\Delta\Delta G^{\ddagger b}_{AB}$, kcal/mole
1	$\phi CH_3HC\text{-}COCH_2C(CH_3)_3$	$LiAlH_4$	ether	35	56/44	-.150
2	"	"	"	0	55.3/44.7	-.110
3	"	"	"	-12	54/46	-.086
4	"	"	"	-20	53.4/46.6	-.066
5	"	"	"	-40	52.7/47.3	-.052
6	"	"	"	-60	49.5/50.5	+.008
7	$C(CH_3)_3CH_3HC\text{-}COCH_3$	$LiAlD_4$	"	35	54/46	-.100
8	"	"	"	0	51.6/48.4	-.040
9	"	"	"	-70	38.6/61.4	+.190
10	$C(CH_3)_3DCH_3C\text{-}COCD_3$	CH_3MgCl	THF	66	73.5/26.5	-.690
11	"	"	"	35	77.4/22/6	-.750
12	"	"	"	15	67.2/32/8	-.410
13	"	"	"	-15	46/54	+.090
14	"	"	"	-24	35.2/64.8	+.310
15	$CH_3CHOH\text{-}CHO$	C_6H_5Li	ether	35	73/27	-.610
16	"	"	"	0	72/28	-.510
17	"	"	"	-30	70/30	-.400
18	"	"	"	-60	68/32	-.350

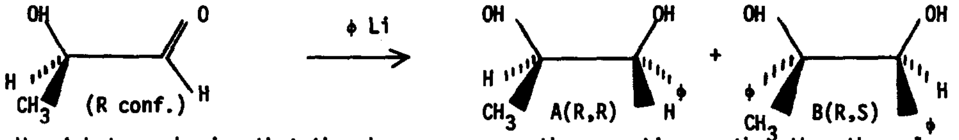
[a] A/B ratios were determined by nmr and whenever appropriate by vpc analyses.

[b] Values are accurate to ± 10%.

kcal/mole is calculated, i.e., enthalpy favors the "wrong" diastereomer B, not A. Similar results were obtained by reducing the ketone with sodium borohydride in isopropyl alcohol.

2. More spectacular are the results given in entries 7-14, i.e., those involving the reduction of 3,4,4-trimethyl-2-pentanone with lithium aluminum deuteride (7-9), and those involving the addition of methylmagnesium chloride in tetrahydrofuran to the corresponding tetradeuteroketone (10-14). In both cases diastereomer A predominates at high temperatures and B at low. Again, enthalpy favors B, the "wrong" diastereomer.

3. Entries 15-18 summarize the data from the addition of phenyllithium to R-lactaldehyde to give diastereomers A (R,R configuration) and B (R,S configuration)[2] as shown below. Although the predicted diastereomer A predominates at all reasonably accessible temperatures, $\Delta\Delta H^{\ddagger}_{AB}$ is +.30 kcal/mole, i.e., enthalpy favors the "wrong" diastereomer B, not A.



We wish to emphasize that the above cases are the exceptions rather than the rule. For example, the addition of phenyllithium to 2-phenyl-4,4-dimethyl-3-hexanone in ether at 35°, 0° and -30° gave A/B ratios of 79/21, 81/19 and 84/16, respectively. Both $\Delta\Delta G^{\ddagger}_{AB}$ and $\Delta\Delta H^{\ddagger}_{AB}$ have the same sign and value, ca -.80 kcal/mole. The additions of methylmagnesium bromide in ether or tetrahydrofuran, of methylmagnesium iodide in ether and of methyllithium in ether to 3,4,4-trimethyl-2-pentomone-1,1,1,3-d_4 were normal, i.e., $\Delta\Delta G^{\ddagger}_{AB}$ and $\Delta\Delta H^{\ddagger}_{AB}$ had the same sign and magnitude (ca -.80 to -.9 kcal/mole,) and contrary to the addition of methylmagnesium chloride in tetrahydrofuran reported above. Finally, the addition of methyllithium to R-lactaldehyde in ether from 35° to -60° gave (R,R)-threo-2,3-butanediol/(R,S)-erythro-2,3-butanediol in ratios varying from 60/40 to 66/34. The signs of $\Delta\Delta G^{\ddagger}$'s (-.26 kcal/mole) and $\Delta\Delta H^{\ddagger}$ (-.33 kcal/mole) are the same and as predicted by the model. These comments notwithstanding, the exceptions reported in this article, along with those already in the literature[3], underscore the fact that models of asymmetric induction should be used primarily as starting points for further experimentation and thinking.

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References.

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2. Absolute configuration of the diastereomeric product 1-phenyl-1,2-propanediols was determined by comparing them with the diols obtained from alkaline and acid opening of the (+) *trans*-1-phenylepoxypropane (R_2,R_1 configuration). Addition of phenyllithium to R-lactaldehyde gave 70% (-)*threo*-1-phenylpropanediol (R_2,R_1 configuration) and 30% (+) *erythro*-1-phenylpropanediol (R_2,S_1 configuration). Alkaline hydrolysis of the (+) *trans*-1-phenylepoxypropane gave 100% (+) *erythro*-diol (R_2,S_1 configuration); acid hydrolysis of the same epoxide gave 62% (+) *erythro*-diol and 38% (-) *threo*-diol (R_2,R_1 configuration).
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