

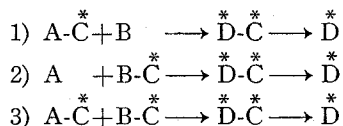
Asymmetric Double Induction

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Additivity of the free energy differences at transition states was tested in asymmetric double induction involving the systems of acrylate with carboalkoxydimethylsulfonium ylid, of acrylate with chloroacetate, of methacrylate with chloropropionate to give chiral cyclopropane products and of pyruvate with acetate to give citramalic acid, all with (–)-menthol used as chiral center. Experiments showed the hypothesis to be valid in systems which gave higher optical yields.

According to the location of chiral centers, conservative asymmetric syntheses are classified schematically in the following 3 types:



In the first type, the chiral center designated as $\overset{*}{C}$ is located in the prochiral substrate molecule A through a covalent linkage and the asymmetric reaction falls in the category of the discrimination between diastereotopic faces or ligands at the prochiral center by achiral reagent B to give diastereomeric products $\overset{*}{D}-\overset{*}{C}$. The second type is just the reverse of the first, constituting an enantioselective reaction in which chiral reagent discriminates between enantiotopic faces or ligands of prochiral substrate. The last is the system which is called "asymmetric double induction" and both the substrate and reagent are chiral due to two or sometimes more chiral centers involved. Chiral centers may not necessarily be centrosymmetric but axial or planar chiroids belonging to either C_n or D_n point group ($n > 1$).

In view of transition state energetics, however, these three asymmetric reactions are all of the same type *i.e.* both transition states leading to respective diastereomer are topologically diastereomeric and are in principle different in free energy ($\Delta\Delta G^\ddagger \neq 0$), eventually resulting in the formation of diastereomeric products in unequal amount.

The transition state energetics of asymmetric reaction, when combined with the schematic classification of conservative asymmetric syntheses provides an interesting concept: the free energy difference of transition states in individual asymmetric syntheses 1) and 2) could be additive in the asymmetric double induction 3).

Should this assumption be valid, the following relationship could hold for a set of appropriately designed asymmetric syntheses:

$$\Delta\Delta G_1^\ddagger + \Delta\Delta G_2^\ddagger = \Delta\Delta G_3^\ddagger \quad (1)$$

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where $\Delta\Delta G_n^*$ represents the free energy difference between diastereomeric transition states in individual system.

Since the following Eq. (2) applies for kinetically controlled asymmetric synthesis in general,

$$\Delta\Delta G^* = RT \ln k_R/k_S = RT \ln R/S \quad (2)$$

the Eq. (3) is derived from (1) and (2),

$$K_1 \times K_2 = K_3 \quad (3)$$

K_n representing the final enantiomeric product ratio R/S in each system. For the sake of experimental convenience, K_n can be substituted by the optical yield p_n , an experimental parameter, and according to the definition,

$$p = (R-S)/(R+S) = (R/S-1)/(R/S+1) = (K-1)/(K+1) \quad (4)$$

the final relationship (5) is obtained, which permits one to test the additivity of free energy differences on experimental level.

$$p_3 = (p_1 + p_2)/(p_1 p_2 + 1) \quad (5)$$

In case that the sense of asymmetric synthesis is reversed in any one of the individual systems, an alternative Eq. (6) must be used with a negative sign arbitrarily given to p_n .

$$p_3 = \pm(p_1 - p_2)/(1 - p_1 p_2) \quad (6)$$

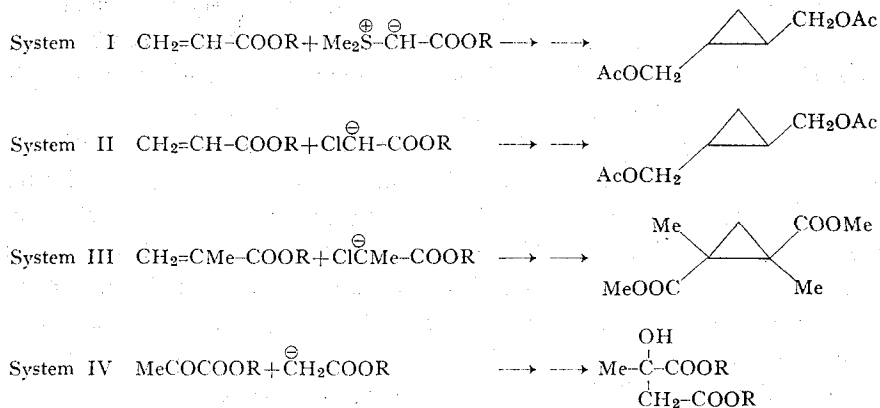
Some examples of double inductions are found in literature,¹⁾ but the reliability of results in earlier works, especially from the quantitative aspects, is difficult to ascertain and the data available for testing the additivity in question are essentially nil. Merely apparent arithmetical additivity¹⁾ of optical yields in individual asymmetric syntheses is not based on a sound kinetic ground, because there is no linear relationship between optical yield (p) and K or $\Delta\Delta G^*$. When the product $p_1 p_2$ in the denominator term of the Eq. (5) and (6) is negligibly small relative to unity, an approximation $p_3 = p_1 \pm p_2$ may be obtained. This treatment, even though mathematically reasonable, is far from being acceptable in chemical meanings. For example, a 5% optical yield ($p=0.05$) at room temperature corresponds to competing asymmetric syntheses which have a difference in their energies of activation of about fifty small calories per mole ($\Delta\Delta G^* = 0.05$ kcal/mole). It is unreasonable to expect that the stereochemical outcome as effected by the free energy difference of such an order can be safely conserved throughout the reaction and subsequent work-up and be reflected in significant optical yield.

Horeau, Kagan²⁾, and Mathieu³⁾ are those who for the first time introduced the concept of additivity of free energy differences on a kinetic basis. They have observed rather negative results in a few cases of double inductions so far studied, but it may be a little bit premature that the hypothesis is doomed to impropriety on charge of failure in limited numbers and types of asymmetric reactions.

It seemed of interest to further studies of asymmetric double induction from quantitative view-point. The system for the test must be such that both substrate (A) and reagent (B) contain a "handle" by which a suitable chiral center ($\bar{C}^*$) may be attached and

detached before and after the reaction.

Designed for this purpose are the reactions of carboalkoxymethyldimethylsulfonium ylid with acrylate (system I), of chloroacetate with acrylate (system II), of chloropropionate with methacrylate (system III), and of pyruvate with acetate (system IV).



The former three systems proceed through the same mechanism, in which the initial nucleophilic attack takes place and the subsequent intramolecular displacement is the rate- and

Table I. Data of Asymmetric Double Induction

System	Type	Location of chiral center ^f	% Yield of chiral product ^g	$[\alpha]_D^{25}(\text{nm})$ (EtOH)	Absol. config.	% p found	% p ₃ calcd
I ^a	1	substrate	35	-2.8 (350)	<i>R</i> : <i>R</i>	8.4	—
	2	reagent	38	+3.6 (350)	<i>S</i> : <i>S</i>	10.5	—
	3	both	30	+0.4 (350)	<i>S</i> : <i>S</i>	1.2	2.1
II ^b	1	substrate	42	-1.5 (350)	<i>R</i> : <i>R</i>	4.4	—
	2	reagent	39	+5.5 (350)	<i>S</i> : <i>S</i>	15.9	—
	3	both	31	+3.2 (350)	<i>S</i> : <i>S</i>	9.4	11.6
III ^c	1	substrate	29	+44.5 (589)	<i>S</i> : <i>S</i>	25.4	—
	2	reagent	32	+14.9 (589)	<i>S</i> : <i>S</i>	8.5	—
	3	both	25	+56.3 (589)	<i>S</i> : <i>S</i>	32.2	33.1
III ^d	1	substrate	32	+49.8 (589)	<i>S</i> : <i>S</i>	28.5	—
	2	reagent	34	+15.2 (589)	<i>S</i> : <i>S</i>	8.7	—
	3	both	29	+59.2 (589)	<i>S</i> : <i>S</i>	33.8	36.2
IV ^e	1	substrate	53	-2.2 ^h (589)	<i>R</i>	11.5	—
	2	reagent	56	+3.4 ^h (589)	<i>S</i>	17.5	—
	3	both	50	+0.8 ^h (589)	<i>S</i>	4.1	6.1

a 0.034 mole scale in 40 ml of methylene chloride.

b 0.02 mole scale in 60 ml of DMF.

c 0.05 mole scale in 50 ml of DMF.

d 0.05 mole scale in 100 ml of DMF.

e 0.026 mole scale in 25 ml of THF.

f (—)-menthol.

g *trans*-*bis* (acetoxymethyl) cyclopropane in systems I and II; dimethyl *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylate in system III; diethyl citramalate in system IV.

h chloroform.

therefore the stereochemical-determining step, equally giving rise to chiral cyclopropanes. The last system is that described by Mitsui and his collaborators,⁴⁻⁶⁾ in which extraordinary high optical yields (70-95%) have been claimed.* (—)-Menthol was used as the chiral center through carboxyl function in both substrate and reagent. Special caution was exercised in working up the reaction products as quantitatively as possible.

Experimental results obtained were summarized in the Table. As can be seen, close similarity of the mechanism and the subsequent work-up was reflected not only in the sense of asymmetric synthesis of the systems I and II but also in the optical yield. Thus, a reversal of steric course** and lower optical yields were observed in both systems. This implies that the steric effect of (—)-menthyl grouping operated in the opposite directions to cancel each other, thus considerably lowering the optical yield in double induction (type 3). This is also the case with system IV involving the aldol type condensation. In contrast, the situation differs in system III and the chiral centers were co-operative to enhance the steric effect in double induction, neither reversal of the sense nor diminution of optical yield having been observed.

Speaking of the additivity in question, an agreement was obtained between the found and the calculated p_3 values, but this is not necessarily satisfactory in systems I, II, and IV, in which the optical yields were too low to be reliable enough to test the proposed hypothesis (*vide supra*).

In case that higher values of optical yield were obtained such as in system III, the additivity of free energy differences seems to be valid to some extent. More experiments of asymmetric double induction of other types are needed for any decisive conclusion to be drawn.

EXPERIMENTAL

Melting and boiling points were uncorrected. Rotations were measured on a Yanagimoto Model ORD-185A recording spectropolarimeter. NMR spectra were taken on a Varian Model A-60 spectrometer, and IR on a Hitachi EPI spectrophotometer.

Carbo-(—)-menthoxydimethylsulfonium Bromide: Vigorous shaking of a mixture of (—)-menthyl bromoacetate (127.6 g; 0.46 mole) and dimethyl sulfide (39 g; 0.63 mole) gave the corresponding bromide, which was recrystallized from ethyl acetate - ether. Yield 90.9 g (58.7%); mp 91.0-92.5°C; IR $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}) 1730, 1600, 1430, 1380, 1315, 1205, 1045, 940, 910, and 845; NMR (CDCl_3) δ (ppm) 3.49 (6H,s, methyl protons on sulfur atom), 5.08 (2H,s, S-CH₂COO): other signals (18H) appeared over the range of δ 0.6-2.5, which were assigned to methyl, methylene, and methine protons in (—)-menthyl moiety.

* Recent re-investigation by French workers⁷⁾ of asymmetric synthesis of aldol type condensation revealed that the higher optical yields reported by the Japanese workers⁴⁻⁶⁾ were in fact due to fractionation during purification of the product acid by means of recrystallizations: moderate optical yields ranging over 30-58% were found for this type of asymmetric syntheses in general, in accord with the data described by Swedish worker⁸⁾ who obtained citramalate in 19-26% optical yields.

** The reversal of steric course found for the reaction types 1 and 2 of the systems I, II, and IV, where the same substrate and reagent with the same chiral center were allowed to react under exactly the same conditions, followed by the same work-up, is worthy of note. Reasonable explanation is to be made for this phenomenon by invoking a possible transition state model for respective system, but this is beyond the scope of our present research concern and will be discussed elsewhere in the future.

(—)-Menthyl (dimethylsulfuranylidene) Acetate: Treatment of the sulfonium bromide (15 g; 0.042 mole) in chloroform with sodium hydroxide solution according to the literature⁹⁾ gave the ylid as an amber yellow oil. Yield 11.4 g (97.6%); IR $\nu_{\text{max}}^{\text{liq.}}$ (cm^{-1}) 1730, 1610, 1450, 1425, 1310, 1125, 1050, 1020, 1000, 808, 863, and 750; NMR (CDCl_3) δ (ppm) 2.78 (6H, s, methyl protons on sulfur atom), 4.6 (1 H, m, proton on the carbon-3 of menthyl residue), 2.9 (1 H, s, proton on the carbanionic center). Other signal (18 H) appeared over the range of δ 0.5–2.4 which were assigned to methyl, methylene, and methine protons in menthyl moiety.

***trans*-1,2-bis (Acetoxymethyl)-Cyclopropane via Sulfonium Ylid (System I)**

The experimental procedure is exemplified by a typical run of the (—)-menthyl (dimethylsulfuranylidene) acetate-(—)-menthyl acrylate in methylene chloride (double induction: type 3 in system I). For the other two individual asymmetric syntheses, the identical procedure was followed with one of the reactants altered.

(—)-Menthyl (dimethylsulfuranylidene)acetate (8.8 g; 0.034 mole) and (—)-menthyl acrylate (7.1 g; 0.034 mole) were allowed to react in 40 ml of methylene chloride at room temperature for 27 hr. After the reaction, solvent was removed under reduced pressure at room temperature and the concentrate was reduced with lithium aluminum hydride (5.0 g; 0.125 mole) in 100 ml of dry ether overnight. Acetic anhydride (30 ml) in ether was added dropwise to the reaction mixture cooled in ice-water and stood still overnight. Aluminum acetate was filtered off and the filtrate was concentrated under reduced pressure. *trans*-1,2-bis(Acetoxymethyl)cyclopropane was isolated pure from the concentrate by means of preparative vpc (Varian Aerograph A-700; 30% Apiezone grease L, 200°C). The IR and NMR spectra of the *trans*-diacetate were identical in every respect with those of the authentic specimen.¹⁰⁾ $[\alpha]_{\text{D}}^{25} + 0.4^\circ$ (c , 5.61, EtOH).

For the asymmetric syntheses in the systems II and III, the experimental procedure was followed in exactly the same manner as described in our previous papers,^{10,11)} except the variation of reaction partners and slight modifications.

For the asymmetric aldol type condensation, the procedure described in earlier literature⁴⁻⁸⁾ was followed with slight modifications and is exemplified by a typical run as follows (type 1):

To a solution of lithium diisopropylamide (30 mmole), prepared from diisopropylamine in THF (30 ml) and *n*-butyl lithium in 15% hexane, kept cooled (-60°C), was added a solution of (—)-menthyl acetate (4.9 g; 26 mmole) in THF (20 ml). After 1.5 hr, ethyl pyruvate (4.0 g; 34 mmole) in THF (5 ml) was added, and after further 40 min. the temperature was allowed to rise to 0°C and the reaction mixture was poured into cold dilute sulfuric acid. The organic layer was separated and water layer was extracted with ether. The combined organic layer and extract was dried over anhydrous sodium sulfate and volatile components were removed off and then hydrolyzed with potassium hydroxide solution under reflux overnight. Water was added and the reaction mixture was washed thoroughly with ether. The aqueous layer was acidified, the solvent evaporated, and the residue was treated with diazoethane solution. The organic layer was distilled to give the fraction boiling at $118\text{--}125^\circ\text{C}/23$ Torr. Yield 2.8 g (52.8%). The diester was further purified by means of preparative vpc (Varian Aerograph A-700, TCD detector; Apiezone grease 30%, column temperature 180°C). The IR and NMR spectra were identical in every respect with those of the authentic specimen.⁸⁾ $[\alpha]_{\text{D}}^{25} - 2.2^\circ$ (c ,

3.4, chloroform). Optical yield 11.5% based on the reported maximum rotation 19.4°. ⁸⁾

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