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Stereochemistry of Diels-Alder Reactions at High Pressure. II. Influence of High Pressure on Asymmetric Induction in Condensation of (−)-Di-(*R*)-menthyl Fumarate with Butadiene and Isoprene[1)]

Janusz Jurczak

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland

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The high-pressure Diels-Alder condensation of (−)-di-(*R*)-menthyl fumarate with butadiene and isoprene, followed by reduction of the adducts with lithium aluminium hydride, produced (1*S*,2*S*)-(+)-4-cyclohexene-1,2-dimethanol and (1*S*,2*S*)-(+)-4-methyl-4-cyclohexene-1,2-dimethanol in 6.2—12.8% optical yield, depending on the pressure applied. Results of asymmetric synthesis were discussed in light of the concept of parallel transition states. An interpretation of the thermal and Lewis-acid-catalyzed asymmetric Diels-Alder condensations using (−)-di-(*R*)-menthyl fumarate was proposed.

The Diels-Alder reaction is one of the best known organic reactions.[2)] In recent years the effect of pressure on the course of the (2+4) cycloaddition reaction has been widely studied.[3)] Cycloaddition reactions are characterized by negative values of activation volume ΔV^* defined as the difference between the volume occupied by the transition state and that occupied by the reactants. The large negative activation volume means that the reaction ought to be accelerated by an increase in pressure. Although this concept is very clear and simple from the theoretical standpoint, there are so far few studies dealing with the utilization of high pressure in organic synthesis.[4—6)] This is due to the relative inaccessibility of high-pressure equipment permitting work on a preparative scale.

High-pressure kinetics are much more frequently studied.[3,7,8)] High-pressure kinetics in solution permit observation of the activation volume ΔV^* whose changes are a convenient tool for interpretation of the mechanism of the reaction.

$$\Delta V^* = -RT(\partial \ln k/\partial P)_T$$

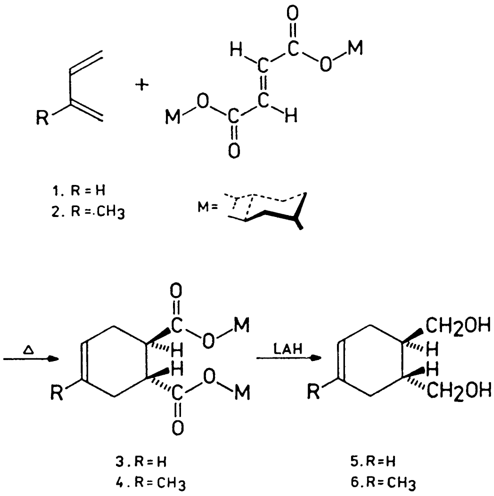
McCabe and Eckert[7)] have shown that the mechanism of the Diels-Alder reaction is of the nature of a concerted process, according to Woodward and Hoffmann.[9)] The (2+4) cycloaddition reaction is characterized by a large negative activation volume, and in some cases the activation volume is more negative than the volume change of reaction, ΔV_r ($\Delta V_r = V_{\text{products}} - V_{\text{reactants}}$). That is, in this case, the transition state is actually more compact than the product, probably due to the occurance of secondary π interactions in the transition state.[10)]

Recently we have observed an effect, heretofore unreported, of high pressure on the direction and magnitude of asymmetric induction in the Diels-Alder condensation of 1-methoxy-1,3-butadiene with (*R*)-(−)-menthyl glyoxylate.[1)] Satisfactory results of these preliminary investigations led us to undertake systematic studies on the effect of high pressure on the stereochemistry of the Diels-Alder reaction, especially on asymmetric induction.

In the present study we report the reaction between butadiene or isoprene and (−)-di-(*R*)-menthyl fumarate. Historically, this is the system for which Korolev and Mur[11)] first demonstrated the possibility of asymmetric induction in diene synthesis in 1948.

Results

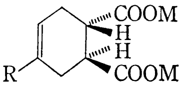
The pioneering work of Korolev and Mur[11)] was repeated and extended by Walborsky *et al.*[12)] who studied the effect of a Lewis acid catalyst on asymmetric induction. Thermal condensation of butadiene or isoprene with (−)-di-(*R*)-menthyl fumarate was carried out by these authors at 25—180 °C in benzene as solvent (Scheme 1).

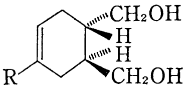


Scheme 1.

Optical yield and the direction of asymmetric induction were studied by measurements of the optical rotation of glycols **5** and **6** whose absolute configurations were established to be (−)-(1*R*,2*R*) by chemical correlations. Specific rotations of pure enantiomers were for **5** $[\alpha]^{23}_{589}$ −70.4° (*c* 3.0, in chloroform) and for **6** $[\alpha]^{25}_{589}$ −78.8° (*c* 3.4, in chloroform). In non-catalyzed reactions carried out at room temperature the products showed no induced optical activity. Elevation of temperature brought about formation of optically active products (0.8% optical yield at 65 °C and 3% at 180 °C), with predominance of the adduct with a 1*R*,2*R* configuration. Longer reaction time increased the total yield of the product, without changing the optical yield. The effect of solvent on the optical yield was slight. Reactions carried out in the presence of Lewis acids afforded predominantly

Table 1. Condensations of butadiene (**1**) and/or isoprene (**2**) with (−)-di-(*R*)-menthyl fumarate in different solvents under high pressure at 25 °C





Diene	Solvent	ΔP/kbar	Yield/%	$[\alpha]^{20}_{589}$ in $CHCl_3$	*c*	Abs. conf.	Optical yield/%
1	$C_6H_5CH_3$	6.9	100	+9.0°	3.14	1*S*,2*S*	12.8
1	CH_2Cl_2	6.9	100	+5.2°	3.22	1*S*,2*S*	7.4
1	CH_2Cl_2	7.4	100	+5.7°	3.14	1*S*,2*S*	8.1
2	$C_6H_5CH_3$	4.0	75	+4.9°	3.20	1*S*,2*S*	6.2
2	$C_6H_5CH_3$	6.1	88	+7.2°	3.22	1*S*,2*S*	9.2
2	$C_6H_5CH_3$	7.5	100	+8.7°	3.05	1*S*,2*S*	11.0
2	$C_6H_5CH_3$	8.4	100	+9.8°	3.00	1*S*,2*S*	12.4
2	CH_2Cl_2	4.5	69	+5.0°	3.08	1*S*,2*S*	6.4
2	CH_2Cl_2	5.9	81	+6.7°	3.10	1*S*,2*S*	8.5
2	CH_2Cl_2	7.0	100	+7.8°	3.27	1*S*,2*S*	9.9
2	CH_2Cl_2	7.8	100	+8.8°	3.34	1*S*,2*S*	11.2

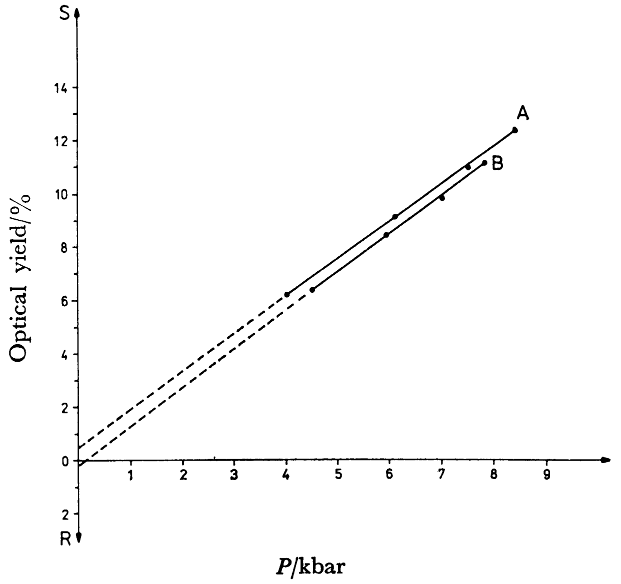


Fig. 1. Dependence of optical yield on pressure in the reactions between isoprene and (−)-di-(*R*)-menthyl fumarate carried out in toluene (A) and dichloromethane (B).

the adducts with opposite absolute configuration, 1*S*,2*S*; optical yields of the asymmetric synthesis were very high—about 75%.

For high-pressure studies of the stereochemistry of the Diels-Alder reaction, earlier observations[13] and preliminary experiments showed that the optimal conditions for the reactions of (−)-di-(*R*)-menthyl fumarate with dienes is at 25 °C and about 7 kbar for 20 h, which afforded a $\sqrt{100}\%$ yield of the product. These conditions were accepted for all high-pressure reactions presented in this study.

In the present studies toluene and dichloromethane were employed as solvents (solidification pressures at room temperature are about 8.8 kbar and about 8 kbar, respectively). We selected these two solvents also because previous work[14] showed that there is a change in the direction of asymmetric induction in the Diels-Alder reaction of 1-methoxy-1,3-butadiene with (*R*)-(−)-menthyl glyoxylate upon changing from an aromatic solvent to dichloromethane or chloroform. Results are presented in the Table showing the yields of adducts **3** or **4**, optical yields and configurations at C-1 and C-2.

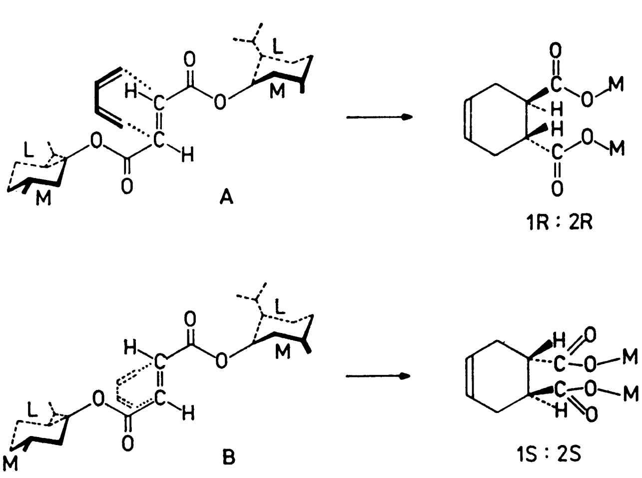
The reaction of butadiene (**1**) with (−)-di-(*R*)-menthyl fumarate in toluene or dichloromethane at approximately 7 kbar gives adduct **3** in a quantitative yield. In all cases *S* configuration is induced at C-1 and C-2; the optical yield is higher in toluene than in dichloromethane. For systematic studies of the effect of pressure on the optical yield of the reaction, isoprene (**2**) was selected as a solvent. In all four reactions carried out in toluene (4.0—8.4 kbar), we obtained product **4** with predominance of the diastereomer of 1*S*,2*S* configuration. The optical yield increased from 6.2% at 4.0 kbar to 12.4% at 8.4 kbar. Similar results were obtained in reactions carried out in dichloromethane. Comparison of the dependence of optical yield on pressure in both solvents is presented graphically in Fig. 1.

The plots clearly testify to the same linear nature of the dependence of optical yield on pressure for both solvents; under the same pressure, optical yields are somewhat higher in toluene than in dichloromethane.

Discussion

Walborsky[12] has accepted the conformational model of Prelog[15] for (−)-di-(*R*)-menthyl fumarate as well as the concept of a rigid transition state in the Diels-Alder reaction[2] (Scheme 2).

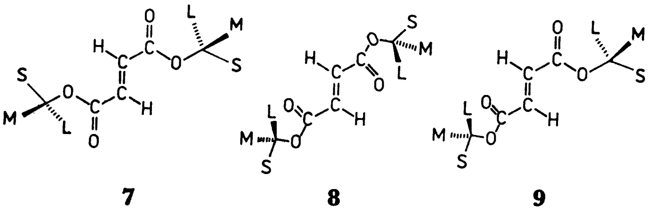
The dienophile and diene approach each other in parallel planes, which results in two possible transition states of the reaction: "A", in which the diene is situated above the dienophile plane from the side of the smaller substituent M, giving an adduct of 1*R*,2*R* configuration, and "B", in which the diene is situated



Scheme 2.

under the dienophile plane, from the side of larger substituent L, giving an adduct of 1*S*,2*S* configuration. The optical activity of the product is due to the difference in the steric ease of mutual approach of the reactants from one or the other side.

Conformational analysis of dienophile leads to the conclusion that three low-energy conformations are prefered: *s-trans*, *s-trans* (**7**), *s-cis*, *s-cis* (**8**), and *s-trans*, *s-cis* (**9**) (Scheme 3). Transoid-transoid conformation **7** prefers the approach of diene "from above," yielding the 1*R*,2*R* product. Cisoid-cisoid conformation **8** brings about formation of the 1*S*,2*S* product. In case of the transoid-cisoid conformation **9**, no asymmetric induction can be expected in reactions with symmetric dienes (*e.g.* butadiene).

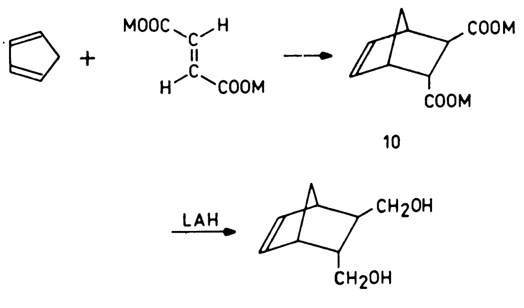


Scheme 3.

Acceptance of the concept of parallel transition states, as proposed by us,(14) permits elucidation of the stereochemical course of asymmetric diene synthesis, without severe deviation from the rules of Prelog(15) and Cram.(16)

For interpretation of the present results of condensations at room temperature, we assume that the optical yield is the result of the population of conformers **7** and **8** in the ground state. It is intuitively obvious that the probabilities of formation of transition states with the participation of conformers **7** and **8** are almost the same, and thus the difference between the activation energies of both transition states is only slight. Therefore, asymmetric induction should depend on the population of conformers **7** and **8**, which at constant temperature ought to be affected by the solvent used. Indeed, we found differences between the absolute configuration and optical yields of the products of the reaction of isoprene with (—)-di-(*R*)-menthyl fumarate run in toluene (2*S*,6*S*, 0.6%) and in dichloromethane (2*R*,6*R*, 0.4%);(17) this seems to confirm the accepted assumption.

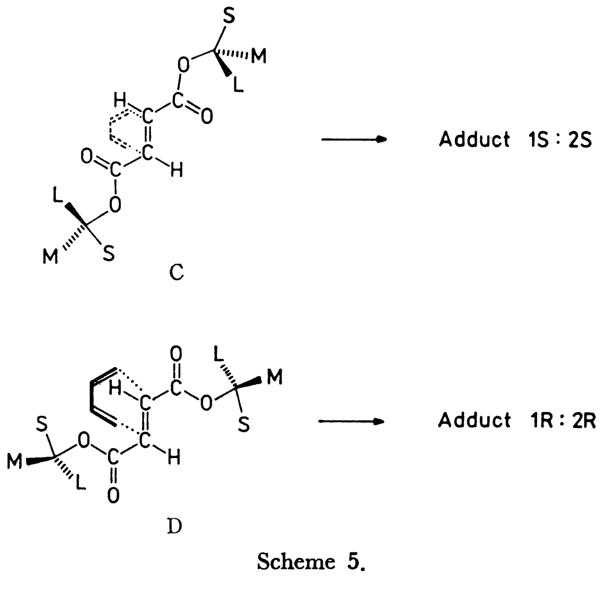
Similar results have been obtained by Sauer and Kredel(18) in reactions of cyclopentadiene with (—)-di-(*R*)-menthyl fumarate (Scheme 4), carried out at 35 °C in several solvents. Using acetone and dioxane, these authors have obtained product **10** with optical yields of 2.8% and 1.5%, respectively; the resulting glycols **11** were dextrorotatory. Upon use of dichloromethane, the optical yield was 3.6%, and the resulting glycol was levorotatory.



Scheme 4.

Results of the high-temperature condensations of Walborsky(12) can be interpreted using the above concept. Elevation of temperature changes the conformational equilibrium of the dienophile, in this case in favor of transoid, transoid form **7**, which is responsible for the formation of the adduct of 1*R*,2*R* configuration. The tendency for an increase in optical yield with elevation of temperature(12) confirms our interpretative approach.

In high-pressure reactions we obtained, irrespective of the solvent, adducts of 1*S*,2*S* configuration, with optical yields much higher as compared with atmospheric-pressure reactions carried out at the same temperature. Optical yields increase distinctly with an increase in pressure. We shall consider these facts in light of the concept of parallel transition states(14) (Scheme 5).



Scheme 5.

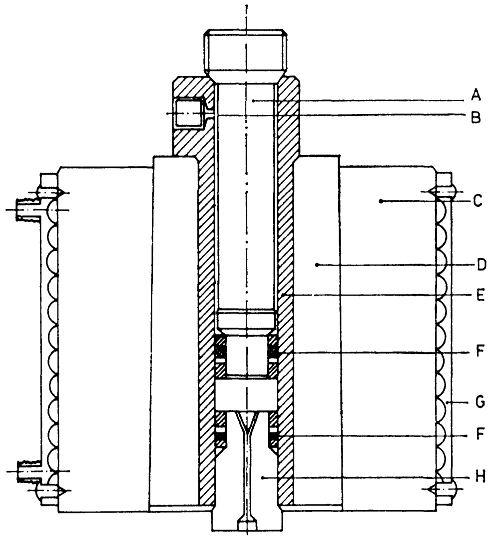


Fig. 2. Sketch of high-pressure apparatus.

Induction of the 1*S*,2*S* configuration in the high-pressure reaction indicates clearly that the active complex of the "C" type is favored, which suggests that it is more compact than "D". The probability of formation of active complex "C" increases with increasing pressure which is in practice the sole parameter determining the optical yield.

The direction of asymmetric induction in high-pressure reactions is identical to that in the reactions catalyzed by Lewis acids; in either case adducts of absolute 1*S*,2*S* configuration are formed. This may suggest that in both cases transition states of a similar type, *i.e.* with a cisoid-cisoid conformation of the dienophile, are preferred.

This conclusion is supported by high-pressure studies of the catalyzed Diels-Alder reaction between 2,3-dimethyl-1,3-butadiene and butyl acrylate, carried out by Poling and Eckert.[19] According to these authors, the activation volume for the reaction catalyzed by $AlCl_3$ is $\Delta V^{*} = -25.7\ cm^3/mol$ and for the non-catalyzed reaction it is $\Delta V^{*} = -28.6\ cm^3/mol$. Comparison of these two values clearly points to similarities in the structures of the transition states of both reactions.

Experimental

Bps refer to air-bath temperatures. Mps (uncorrected) were determined on a Kofler block. Polarimetric measurements were performed with a Perkin-Elmer 141 automatic polarimeter. Silica gel G Merck was used for TLC, and silica gel 100—200 mesh Macherey-Nagel for column chromatography. All reactions and chromatographic separations were monitored in TLC. All high-pressure reactions were carried out in a piston-cylinder type apparatus. Initial working volume was about 10 ml. The details of this apparatus, previously applied to various investigations on the metal-hydrogen system,[20,21] are presented in the Fig. 2. The internal part (E) consisted of a beryllium brass vessel supported by two external steel rings (C,D). A jacket (G) supplied by flowing water served thermostatic conditions. It could be maintained within ±1 °C. The electrical leads for pressure and temperature measurements (manganine manometer, thermocouple) were led through a conical electrode placed in the stopper (H) of beryllium brass. The mobile piston (A) was made of special steel composition with an ending of beryllium brass. The sealing (F) of the mobile piston and the stopper was conventional character (O-ring and metallic Bridgeman type sealing) as described previously[22]. The reaction can be done under any gaseous atmosphere. The gas was introduced into the working volume through the capillary inlet (B), being initially compressed to 1—1.5 kbar in a separate multiplier.[21] The pressure inside the working volume was measured by a calibrated manganine coil with accuracy ±0.1 kbar.

Butadiene and isoprene were redistilled commercial (Fluka) reagents. (−)-Di-(*R*)-menthyl fumarate was prepared according to earlier procedure,[11] mp 59—60 °C, $[\alpha]^{20}_{589}$ −103.1° (*c* 1.55, in chloroform).

Condensations of butadiene and/or isoprene with (−)-di-(*R*)-menthyl fumarate.

Partial asymmetric synthesis of *trans*-4-cyclohexene-1,2-dimethanol (**5**) and *trans*-4-methyl-4-cyclohexene-1,2-dimethanol (**6**) was effected using both the atmospheric- and high-pressure methods.

Procedure A; *Atmospheric-pressure Method.* To a solution of 1.96 g (5 mmol) (−)-di-(*R*)-menthyl fumarate and 10 mg hydroquinone in 20 ml of toluene, 0.68 g (10 mmol) isoprene was added and the mixture was left at room temperature for 300 h. Solvent was removed and residue was dissolved in anhydrous ether and added to a refluxing slurry of 2.2 g (6 mmol) lithium aluminium hydride in 100 ml anhydrous ether. The reaction mixture was dried ($MgSO_4$) and filtered. The solvent was evaporated and the product isolated by column chromatography. Menthol was eluted using a mixture of ligroin and ether (9 : 1, v/v) and the glycol **6** was eluted using a mixture of ligroin and ether (7 : 3, v/v). After removal of the solvents the residue was distilled to give **6** (70%), bp 128—130 °C/0.2, mp 54—57 °C (from ether).

Procedure B; *High-pressure Method.* The high-pressure apparatus, closed on the bottom with a stopper, was filled with the reaction mixture (2.5 mmol (−)-di-(*R*)-menthyl fumarate, 5 mmol butadiene and 5 mg hydroquinone in 10 ml of dichloromethane) and a mobile piston was inserted. Then the whole assembly was placed between the pistons of a hydraulic press and the pressure was elevated up to 7.3 kbar. After stabilization of the pressure the heater was switched on, whereupon the temperature was raised to 25 °C and pressure to 7.4 kbar. The reaction mixture was kept under these conditions for 20 h. Pressure was released and the solvent was evaporated. The residue (100% yield of adduct **3**) was treated with 1 g (2.7 mmol) of lithium aluminium hydride in anhydrous ether for 12 h and the glycol **5** isolated (78%), bp 103—105 °C/0.2. The glycol **5** solidified on standing, mp 49—53 °C.

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