EFFECT OF PRESSURE ON THE ASYMMETRICAL SYNTHESIS OF ATROLACTIC ACID

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A reaction proceeds asymmetrically due to a difference in the rates of two competitive processes which lead to the development of mirror-image, isomeric, asymmetrical centers; the reason for the nonequivalence of these processes is the difference in their steric hindrances. As a result, the investigation of the effect of pressure on the stereospecificity of an asymmetrical synthesis is intimately bound up with a study of the general principles of the effect of pressure on sterically hindered reactions. The following rule has previously been formulated: the more sterically hindered a chemical reaction, the more it will be accelerated by pressure [1, 2]. According to the model proposed for the explanation of this principle, the Van-der-Waals spheres of repulsing atoms overlap during the formation of the transition state, and this leads to a decrease in the volume [1]. The latter will be even more significant, the greater the steric hindrance of the reaction.

However, in our previous investigation of the effect of pressure on the stereospecificity of the asymmetrical condensation of di-(—)-menthyl fumarate with butadiene [3], we found that the experimental results do not agree with the indicated model. To explain the experimental data it was assumed that steric hindrance leads to a decrease in the free volume as a consequence of a decrease in the conformational mobility of interacting groups of atoms. If this effect prevails over the change in the intrinsic volume postulated by the earlier overlapping-sphere model, one should expect symbatic character in the majority of cases in the changes in $(-\Delta S^{\neq})$ and $(-\Delta V^{\neq})$ rather than in E and $(-\Delta V^{\neq})$, as was observed in [3].

The aim of this study was a further verification of the new hypothesis. A convenient subject for the study was the asymmetrical synthesis of atrolactic acid (AA) by the addition of CH_3MgI to (—)-menthyl phenylglyoxylate (MPG):

$$C_6H_5COCOOC_{10}H_{19} \xrightarrow{CH_3MgI} C_6H_5(CH_3)C^*(OH)\,COOH$$

TABLE 1. Effect of Pressure on the Asymmetrical Synthesis of Atrolactic Acid

P, kg/cm²	Optical rotation $[\alpha]_D^{20}$	Optical rotation $[\alpha]_D^{20}$ av.	Optical yield, %*	Sp
1	—12,4 —11,8 —11,8	—12,0	31,8	1,93
1000	—11,2 —11,1	—11,1	29,5	1,84
3000	—10,1	—10,1	26,8	1,73
5000	—9,1 —9,1 —9,2	—9,1	24,2	1,64

*In the calculation, $[\alpha]_D$ —37.7 °C for optically pure AA was used [10].

This reaction was first studied by McKenzie [4], and was then one of the subjects of the classical investigations of Prelog [5, 6]; it was found that the AA form contains an excess of the (—)-isomer. It was recently established [7] that a change in temperature from —95 to +35° does not affect the degree of asymmetrical synthesis and that both competing reactions therefore have the same energies of activation over the indicated temperature range; the stereospecificity, however, is determined by the difference in the $\Delta S^{\neq}$ values $[(\Delta S^{\neq}_{(-)} - \Delta S^{\neq}_{(+)}) = 0.9$ eu]. According to the overlapping-sphere model, pressure should not affect the stereospecificity of this reaction, since the equality of the energies of activation attests to the same values of steric strain, and, as a result of this, also apparently attests to the same overlap volumes. However, according to the new model, one could expect a decrease in the stereospecificity with increasing pressure, since the more rapid formation of the (—)-isomer of AA is characterized by a smaller

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($-\Delta S^{\neq}$) value and, consequently, should have a smaller ($-\Delta V^{\neq}$) value than the reaction to form its antipode. As a consequence, the reaction (which proceeds at a high rate) should be accelerated by pressure to a lesser extent than the second reaction, and the difference in rates should decrease with increasing pressure.

EXPERIMENTAL METHOD

We used MPG obtained by the method in [4] in the experiments: $[\alpha]_D^{20}$ −44.5° (C 1.00, ethanol), mp 70.0-72.5° [$[\alpha]_D^{20}$ −44.7° (C 1.04, ethanol) and mp 71-72° [8]]. Gas–liquid chromatographic analysis of the MPG demonstrated the absence of menthol (LKhM-8M chromatograph, flow meter, 2 m × 4 mm column, silanized Chromosorb W with 15% SKFT-100 silicone, 150°, helium as the gas carrier).

The investigation was carried out at 25° and 1000, 3000, and 5000 kg/cm^2. As a rule, several experiments were accomplished at each pressure. A previously developed technique for mixing the reagents directly under pressure was used [9]. The reaction vessel was a thin-walled Teflon ampul divided into two parts by a thin Teflon film. A solution of 1 g of MPG in 22 ml of absolute ether was poured into the larger part of the ampul, which also contained a compact firing pin. A total of 7 ml of an ether solution of a Grignard reagent, prepared from 0.25 g of Mg and 0.25 g of CH_3I, was poured into the smaller part of the ampul. The ampul was placed in a thermostated high-pressure vessel, which was reversed after supplying the pressure and aging. The firing pin perforated the film in the process, and the solutions were mixed. After aging for 30 min, the ampul was withdrawn. The completion of the reaction was monitored by gas–liquid chromatography (with the column described above at 205-215°) with respect to analysis of the product obtained after decomposition of the Grignard complex. The experiments were treated in accordance with [6], but the menthyl ester of AA was vacuum fractionated prior to saponification to give a material with bp 141-142° (1.5 mm). After thorough drying in vacuo at 60° the AA melted at 92-93° [6]. Found: C 65.05; H 6.21%. $C_9H_{10}O_3$. Calculated: C 65.05; H 6.06%.

The optical rotation was measured with a "Hilger M-412" polarimeter with the light of a sodium lamp with an accuracy of ±0.01° in a 1 dm long tube in absolute alcohol (C 3.0 to 6.0). Each sample was analyzed twice, including preparation of a solution and measurement of the optical density. The specific rotation of the AA obtained by this experimental method coincided with the value obtained in the usual experiment in a glass apparatus. Changing the location of the reagents in the ampul did not affect the results.

DISCUSSION OF RESULTS

The experimental results are presented in Table 1. The $[\alpha]_D^{20}$ values that we obtained at atmospheric pressure were somewhat higher than the values presented in [6] (−9.6°) but close to the values obtained in [4, 8] (−11.0 to −11.5°). These differences are apparently due to the degree of drying of the AA. To check the stability of the reaction product under pressure the ampul was held for 1 h at 5000 kg/cm^2 after carrying out the reaction at atmospheric pressure. The AA obtained after experimental treatment had $[\alpha]_D^{20}$ −11.4°, which lies within the limits of experimental error at atmospheric pressure. Thus the $[\alpha]_D^{20}$ values obtained reflect the true, kinetically monitorable stereospecificity of the reaction. The stereospecificities, $Sp = k_{(-)}/k_{(+)}$, calculated from the formula $Sp = (100 + p)/(100-p)$, where p is the optical yield in percent, are given in the last column of Table 1.

The stereospecificity decreases with increasing pressure, which should have been expected from the hypothesis of the relationship between steric hindrance and the decrease in the free volume. The dependence of log Sp on pressure is expressed by a smooth curve. The volume effect of stereospecificity, $\Delta\Delta V^{\neq}_{st} = (\Delta V^{\neq}_{(-)} - \Delta V^{\neq}_{(+)}) = (V^{\neq}_{(-)} - V^{\neq}_{(+)})$, was calculated by means of the equation

$$\left(\frac{\partial \ln Sp}{\partial P}\right)_T = -\frac{\Delta\Delta V^{\neq}_{st}}{RT}$$

with respect to the slope of the P = 0 curve and was found to be 1.2 cm^3/mole.

In our previous paper [3], starting from the hypothesis of the relationship between the steric hindrance and the change in the free volume, we formulated a rule, according to which the pressure should promote an increase in the stereospecificity if the isomer that is formed in excess is characterized by a lower preexponential factor in the Arrhenius equation than that of its diasteromer. If this is not the case, the pressure should decrease the stereospecificity. In accordance with this rule, we observed both cases: a decrease in the stereospecificity for the reactions studied in this paper, and an increase in the stereospecificity with increasing pressure for the reaction of di-(—)-menthyl fumarate with butadiene [3].

CONCLUSIONS

1. A decrease in the sterospecificity of the asymmetrical addition of methylmagnesium iodide to (–)-menthyl phenylglyoxylate on increasing the pressure to 5000 kg/cm^2 was found.

2. The hypothesis, according to which the additional accelerating effect of pressure in sterically hindered reactions is due to a decrease in the free volume, was confirmed; the latter is due to the restriction of the conformational mobility of the interacting groups of atoms during the formation of the transition state.

3. The previously formulated rule which determines the effect of pressure on the stereospecificity of asymmetrical synthesis was confirmed.

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