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ORGANIC REACTIONS UNDER HIGH PRESSURE

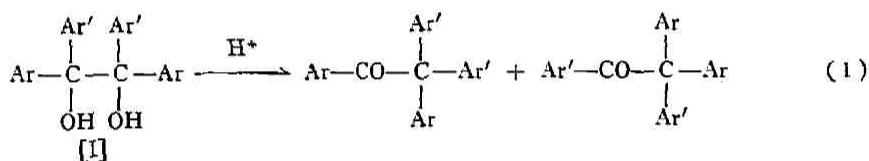
I Pressure and Solvent Effects on the Migratory Aptitude of *o*-Anisyl Group

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The migratory aptitude of the *o*-anisyl group in the pinacol rearrangement of 2,2'-dimethoxybenzopinacol is changed by pressure and solvents. The increasing pressure retards the migration of the *o*-anisyl group in acetic acid and acetonitrile. And the migratory aptitude increases with the changes of solvents in the order of acetic acid < acetonitrile < toluene. These observations indicate that the migration of the *o*-anisyl group brings about higher degree of desolvation than the migration of the phenyl group. This is attributable to steric inhibition of solvation and the difference of charge distribution in the two transition states.

Introduction

Bachmann¹⁾ and Beale²⁾ investigated the pinacol rearrangement of symmetrically substituted benzopinacol derivatives [I] in acetic acid (equation 1) and they found that the migratory aptitudes of *p*-substituted phenyl groups are in the order of relative rates of aromatic substitution of the corresponding monosubstituted benzenes (Table 1). However, the migratory aptitude of the *o*-anisyl group was abnormally low.



Ar, Ar' : monosubstituted phenyl group

Table 1 Migratory aptitudes of monosubstituted phenyl groups in [I]

substituents		substituents	
<i>p</i> -methoxyl	500	<i>p</i> -iodo	1.0
<i>p</i> -methyl	15.7	<i>p</i> -bromo	0.7
<i>p</i> -phenyl	11.5	<i>p</i> -chloro	0.66
<i>p</i> - <i>iso</i> -propyl	9	<i>o</i> -methoxyl	0.3

(phenyl=1)

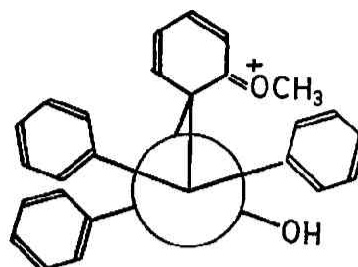
However, no effort has been made to rationalize the reason of retardation of the *o*-anisyl migra-

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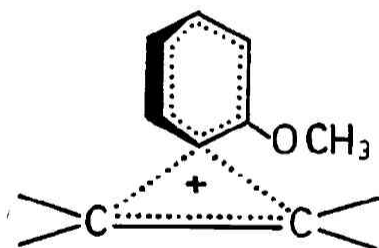
- 1) W. E. Bachmann and J. W. Ferguson. *J. Am. Chem. Soc.*, **56**, 2081 (1934)
- 2) C. H. Beale and H. H. Hatt. *ibid.*, **54**, 2045 (1932)

tion. The low migratory aptitude of *o*-anisyl group is ascribed to steric interference between the *o*-methoxyl group and the nonparticipating aryl groups in the transition state [II]³⁾. There has been an open question, what is meant by the term "steric interference".

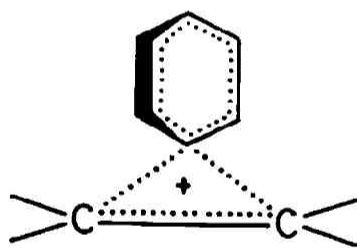
Hamann⁴⁾ and Gonikberg⁵⁾ studied about the effects of pressure on a number of organic reactions and they found that the accelerating effect of pressure upon the rate of a series of organic reactions, in general, increases with increasing geometrical complexity of the transition states. The most plausible explanation of such a change is Gonikberg's suggestion that ΔV^{\ddagger} contains a negative term $\Delta V^{\ddagger}_{steric}$ arising from the overlap of interfering atoms in the transition states. Accordingly, if the reason for the retardation of the *o*-anisyl migration is the purely sterical repulsion between the *o*-methoxyl group and the nonparticipating aryl groups in the transition state [II], it should be expected that the increasing pressure accelerates the migration of the *o*-anisyl group or at least does not affect it. If the effect of pressure is in the opposite direction, there must be other factors which make the transition state of the *o*-anisyl migration [III] less stable than that of the phenyl migration [IV] in addition to the purely sterical repulsion between substituents.



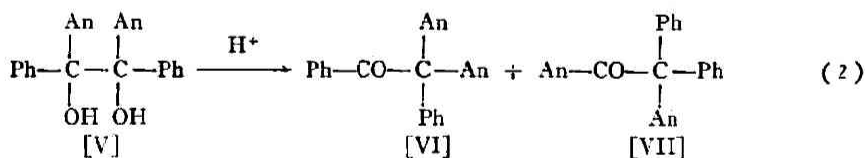
[II]



[III]



[IV]



An: *o*-anisyl group. Ph: phenyl group

[V]: 2, 2'-dimethoxybenzopinacol

[VI]: 2, 2'-dimethoxytrityl phenyl ketone

[VII]: 2-methoxytrityl *o*-anisyl ketone

- 3) For example, E. S. Gould, "Mechanism and Structure in Organic Chemistry", p. 609, Henry Holt and Company, Inc., New York (1960)
- 4) S. D. Hamann, *Ann. Rev. Phys. Chem.*, **15**, 353 (1964)
- 5) M. G. Gonikberg, "Chemical Equilibrium and Reaction Rates at High Pressures", p. 106, Izdatel. Akad. Nauk, SSSR, Moscow, (1960) [English transl. Israel Program for Scientific Translations, Jarusalem]

This publication concerns the effects of pressures and solvents on the migratory aptitude of the *o*-anisyl group of meso and racemic 2,2'-dimethoxybenzopinacols [V] (equation 2) in order to clarify the nature of the so-called *ortho* effect in pinacol rearrangement.

Experimentals

Materials

2, 2'-Dimethoxybenzopinacol was prepared by the method of Beale and Hatt from 2-methoxybenzophenone. Meso form and racemic form⁶⁾ were separated by thin layer chromatography*1 (silicagel, *n*-hexane : benzene = 1 : 3 v/v), mp 189~190°C (meso), 178~179°C (racemic). Acetic acid, acetonitrile, and toluene were commercial materials and purified by the ordinary method. Chloroform was commercial analytical reagent. Guaranteed reagent grade *p*-toluenesulfonic acid monohydrate was used as catalyst after drying under vacuum at room temperature. When anhydrous *p*-toluenesulfonic acid was desired, the acid monohydrate was dehydrated by heating to 55~60°C under vacuum in the presence of phosphorous pentoxide for a week⁷⁾.

Apparatus

The high pressure equipment is shown in Fig. 1. The glass hypodermic syringe, which contained

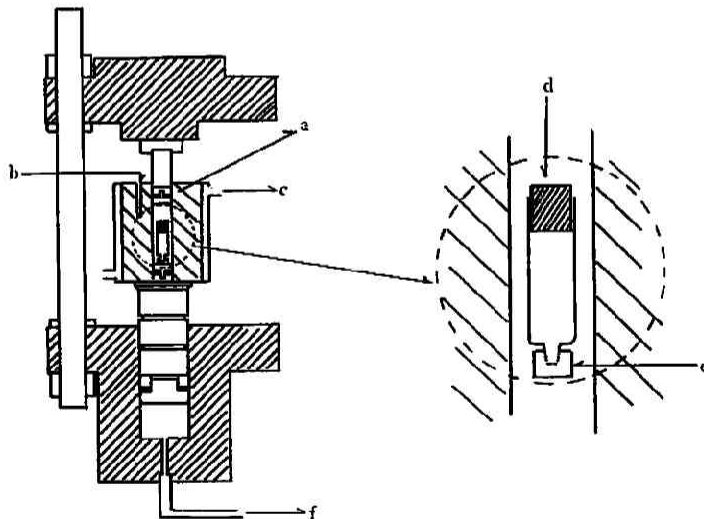


Fig. 1 The high pressure equipment
a, pressure vessel; b, thermocouple; c, thermostatted water; d, glass syringe; e, "Teflon"; f, to plunger-pump

* 1 Silicagel was suspended in 0.04% uranine aqueous solution instead of distilled water.

6) R. Goto, A. Sera and K. Matsumoto, *Nippon Kagakuzasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **86**, 96 (1966)

7) F. Kraft and W. Wilke, *Ber.*, **33**, 3208 (1900)

the reaction solution, was put in the cylindrical pressure vessel, and pressure was applied through the intensifier by means of a plunger-pump. The reaction temperature was kept at 77.4°C by allowing the thermostatted water to circulate around the pressure vessel and was measured by a copper-constantan thermocouple inserted in b.

Rearrangement

In acetic acid: To 4 ml of 0.0047 M pinacol solution, 1 ml of 0.43~0.44 N *p*-toluenesulfonic acid monohydrate solution was added at room temperature and the mixture was quickly transferred to a hypodermic syringe. The syringe was put in the preheated pressure vessel and pressurized. After the reaction was completed, the syringe was taken out and the reaction mixture was diluted by adding water. The white precipitate was collected and washed with distilled water and dried under vacuum.

In acetonitrile: With 1 ml of 0.12 N anhydrous *p*-toluenesulfonic acid solution, 4 ml of 0.0047 M pinacol solution was mixed at room temperature and treated as in the case of acetic acid. The reactions at atmospheric pressure were carried out in a sealed tube which was immersed in a thermostat (77.4±0.02°C).

In toluene: To 8.1~8.3 mg anhydrous *p*-toluenesulfonic acid weighed into a glass stoppered test tube, 4 ml of toluene was added and kept in the thermostat for a few hours in order to dissolve the acid completely. After complete dissolution, 1 ml of 0.019 M pinacol solution was added and the test tube was kept in the thermostat until the reaction was almost completed. The reaction mixture was washed three times with distilled water and toluene was removed under reduced pressure.

Analysis

A mixture of produced ketones [VI] and [VII] was dissolved in chloroform and separated by thin layer chromatography (silicagel, benzene)⁸⁾. Each ketone was extracted by 10 ml of chloroform and the concentration was determined by UV spectroscopy. Physical constants of ketones were given in Table 2.

Table 2 Physical constants of reaction products

compounds	Rf. ^{a)}	mp (°C)	$\lambda_{\max}^b)$	$\epsilon^b)$
[VI]	0.3	206.7~207.3	276 m μ	5340
[VII]	0.2	180.0~180.6	281.5m μ	3900

a) silicagel, benzene b) in chloroform

It was confirmed by thin layer chromatography that both ketones were stable under all the conditions employed.

Results and Discussion

Migratory Aptitude: The migratory aptitudes of the *o*-anisyl group*² (phenyl=10) in acetic acid

8) K. Matsumoto, R. Goto and T. Asano, *Nippon Kagakuzasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, 86, 1076 (1966)

* 2 The migratory aptitude is defined as (moles of [VI]/moles of [VII]) × 10

under various pressures are given in Table 3.

Table 3 Effect of pressures on the migratory aptitude of the *o*-anisyl group of [V] in acetic acid^{a)}

<i>P</i> (kg/cm ²)	1	1000	2000	3000
meso	3.73	3.39	3.19	3.09
racemic	3.24	2.95	2.74	2.65

a) temperature 77.4°C, *p*-toluenesulfonic acid 0.085~0.088 N

The above results indicate that the application of pressure gives rise to increased phenyl migration. As it is reasonable to assume that the migratory aptitudes are the relative migration rates of the *o*-anisyl group to the phenyl group, from the results in Table 3, Fig. 2 is obtained, in which k_{Ph} is the rate of migration of the phenyl group and k_{An} is that of the *o*-anisyl group. A difference of the activation volumes of the migration steps (product determining steps) at zero pressure, $\partial \Delta V_0^\ddagger = \Delta V_0^\ddagger_{Ph} - \Delta V_0^\ddagger_{An}$ ^{*3}, can be calculated from the slope of Fig. 2 at zero pressure.

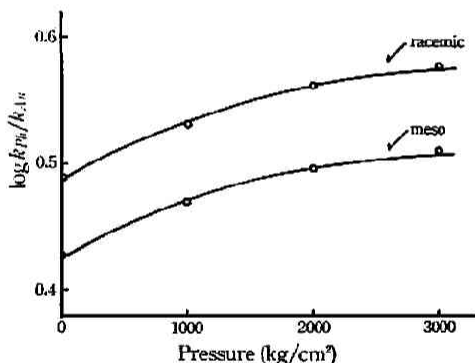


Fig. 2 Plot of $\log(k_{Ph}/k_{An})$ vs. pressure obtained from the results in Table 3

The curves give $\partial \Delta V_0^\ddagger = -3.4 \pm \sim 0.5$ ml/mole in both isomers. Apparently, these results show that there should be some effects retarding the migration of the *o*-anisyl group besides the purely steric repulsion between the *o*-methoxyl group and the nonparticipating aryl groups.

The effect of pressures on the migratory aptitudes in acetonitrile is shown in Table 4 and Fig. 3.

Table 4 Effect of pressures on the migratory aptitude of the *o*-anisyl group of [V] in acetonitrile^{a)}

<i>P</i> (kg/cm ²)	1	1000	2000	3000
meso	5.47	4.96	4.60	4.40
racemic	4.70	4.17	3.90	3.37

a) temperature 77.4°C, *p*-toluenesulfonic acid 0.023 N

$$*3 \left(\frac{\partial \ln k_{Ph}/k_{An}}{\partial P} \right)_T = \left(\frac{\partial \ln k_{Ph}}{\partial P} \right)_T - \left(\frac{\partial \ln k_{An}}{\partial P} \right)_T = -\frac{1}{RT} (\Delta V^\ddagger_{Ph} - \Delta V^\ddagger_{An})$$

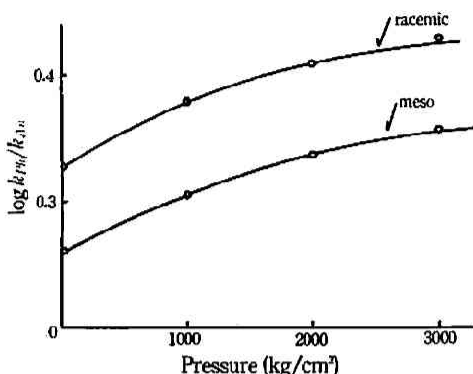


Fig. 3 Plot of $\log(k_{PA}/k_{AN})$ vs. pressure obtained from the results in Table 4

Although the *o*-anisyl migration is easier compared with that in acetic acid, the pressure effect is in the same direction and magnitude as in acetic acid. From the slopes in Fig. 3, $\partial \Delta V_0^\ddagger = -3.4 \pm \sim 0.5$ (meso) and $-4.0 \pm \sim 0.5$ (racemic) ml/mole are obtained respectively.

The results in Tables 3 and 4 are summarized as follows.

(i) In both solvents, the migratory aptitude of the *o*-anisyl group of meso form is greater than that of racemic form.

(ii) In both solvents, the *o*-anisyl migration is retarded with increasing pressure.

(iii) A difference of the migratory aptitudes of meso and racemic form does not change with pressure. That is, the pressure effect is equal upon both isomers.

(iv) Acetonitrile facilitates the *o*-anisyl migration compared with acetic acid*⁴.

The isomerization of the pinacols under reaction conditions is shown in Table 5*⁵.

Table 5 Isomerization of the pinacols observed under reaction conditions

solvents	ordinary pressure	high pressure
acetic acid	meso \rightleftharpoons racemic	meso \rightleftharpoons racemic
acetonitrile	meso \rightleftharpoons racemic	meso \rightleftharpoons racemic
toluene	meso \rightleftharpoons racemic	meso \rightleftharpoons racemic

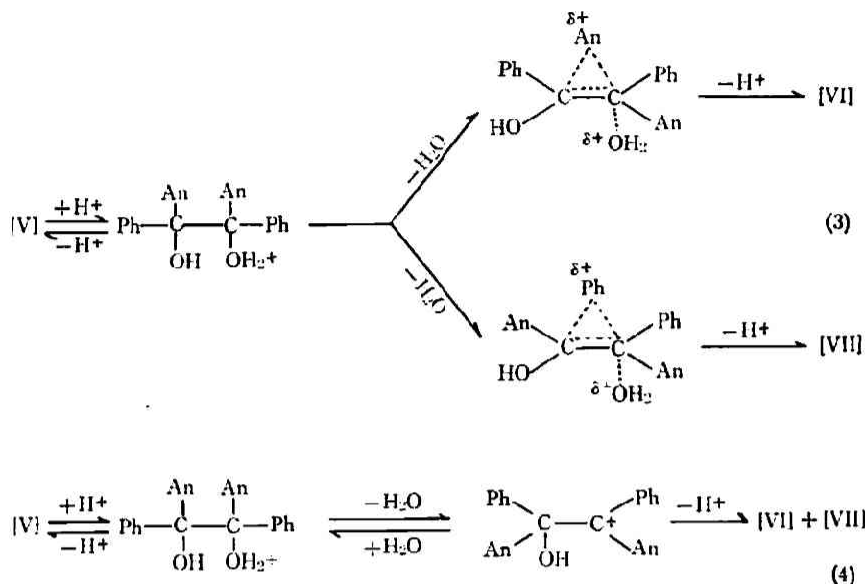
The facts that the migratory aptitudes are different in meso and racemic form and that the racemic pinacol does not isomerize under all the conditions used suggest that this reaction proceeds, in general, as in equation (3)*⁶. It may be considered, however, that some portion of meso form rearranges by the way of equation (4) under some conditions. The details of the reaction mechanisms and the reasons for

* 4 A concentration of catalyst, *p*-toluenesulfonic acid, was shifted to 0.088 N, but the migratory aptitude did not change. The values at 1 atm were 5.47 (meso) and 4.66 (racemic).

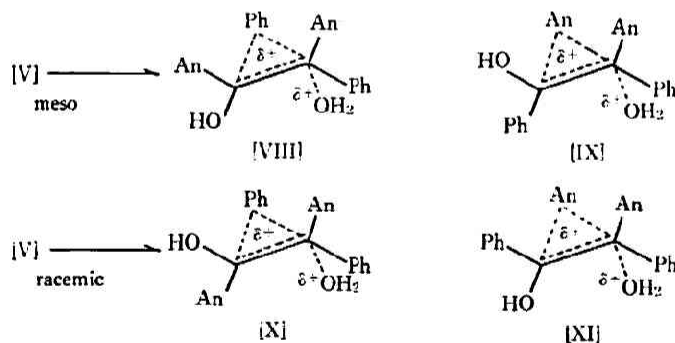
* 5 The isomerizations were confirmed by thin layer chromatography.

* 6 In benzopinacol, Gebhart⁹⁾ suggested equation (4) on the basis of the relatively large value of ΔS^\ddagger . However, taking into consideration the contribution to the entropy of activation from desolvation accompanied by the migration of the phenyl group, his suggestion seems to be uncertain or doubtful.

9) H. J. Gebhart Jr., *J. Am. Chem. Soc.*, **76**, 3925 (1954)



the different behaviors of meso and racemic form remain uncertain and should be elucidated in further investigation. According to the above considerations, the different migratory aptitudes in two isomers are most plausibly explained by the difference of the eclipsing of nonparticipating substituents in the transition states [VIII]~[XI].



In the transition state [VIII], which is formed from meso pinacol with a participating phenyl group, the largest substituents, the *o*-anisyl groups are cis. On the other hand, in [X], from racemic pinacol with a participating phenyl group, two *o*-anisyl groups are trans. Therefore, [VIII] should be less stable than [X]. Considering transition states with a participating *o*-anisyl group, [IX] and [XI], [IX], from meso form, should be more stable than [XI], from racemic form, because in [IX] the largest *o*-anisyl group and the smallest hydroxyl group are cis but in [XI] the *o*-anisyl group and the phenyl group are cis. For this reason, the migratory aptitude of the *o*-anisyl group should be larger in meso form than in racemic form. This prediction seems to be in accordance with what has been observed.

Pressure Effect: From the value of $\delta\Delta V^{\ddagger}$, the volume of transition state [III] is larger than that of [IV] by about 3~4 ml/mole in acetic acid and acetonitrile at 1 atm. As mentioned in the introduction, these differences should not be present in pinacol molecule itself, but rather in solvated species. Moreover, the fact that the pressure effect upon two isomers is equal indicates that the volumes of transition states are not affected by the configuration of nonparticipating substituents.

Solvent Effect: Some desolvation will be expected to occur during the rearrangement of an aryl group, because of both steric and electronic changes in the molecule. The large configurational transformation of the pinacol molecule should require the reorganization of solvation sphere, because the solvent molecules should rearrange their packing for the purely sterical reasons to accommodate the changed shape of the reacting molecules. An alternative way to state this interpretation is to say that the solvent molecules attached to positively charged part of the reactant or to methoxyl oxygen atom (especially in acetic acid), are excluded by an attacking aryl group. For they interfere its approach. Moreover, the spreading of positive charge over the migrating aryl group should cause the loosening of the electrostatic interaction between the solvent and the reactant species. The degree of desolvation should be larger in *o*-anisyl migration than in phenyl¹⁰⁾. For the *o*-methoxyl group—its position is close to the reaction center and hence the repulsion between the substituents must be larger—should require a larger transformation of the geometrical shape of the reacting molecule. And also the positive charge might spread over this substituent for its electron releasing nature.

The experimental results in toluene make this interpretation plausible. The migratory aptitudes of the *o*-anisyl group in toluene are 6.40 (meso) and 6.00 (racemic), respectively, at 1 atm (77.4°C, *p*-toluenesulfonic acid 0.0096 N). These large values should be expected from the low solvating power of toluene. That is, in toluene because of its low solvating power, the destabilization of the transition states [VIII]~[XI] by desolvation might be small. Accordingly, the free energy difference between [VIII] or [X] and [IX] or [XI] should become smaller than in more polar solvents, acetic acid and acetonitrile. Although higher degree of desolvation is considered to cause the abnormally low migratory aptitude of the *o*-anisyl group, the difference in charge distribution in the two transition states [IX] or [XI] and [VIII] or [X] is not the sole reason for this higher degree of desolvation. If it is the only one reason, the migratory aptitude of the *o*-anisyl group should become smallest in acetonitrile which has the largest dielectric constant 37.5 (20°C). However, in practice, the migration of the *o*-anisyl group is retarded most highly in acetic acid. Accordingly, the higher degree of desolvation in the transition state [IX] or [XI] compared with [VIII] or [X] must be attributed mainly to steric factors: steric inhibition of solvation by the *o*-methoxyl group.

From the above discussion, we are now strongly inclined to maintain that besides the stability of the reacting molecule itself the difference in solvation of transition states must be considered in discussing the low migratory aptitude of the *o*-anisyl group in the pinacol rearrangement of meso and racemic 2,2'-dimethoxybenzopinacol.

10) That an *o*-substitution causes steric inhibition of solvation has been reported, *e.g.* (a) N. B. Chapman, J. Shorter and J. H. P. Utkey, *J. Chem. Soc.*, 1963, 1291 (b) W. J. leNoble, *J. Am. Chem. Soc.*, 85, 1470 (1963)

Acknowledgment

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