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Boron Trifluoride Hydrate-catalyzed Competitive Benzylation of Benzene and Toluene with Benzyl and Substituted Benzyl Chlorides

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The competitive benzylation of benzene and toluene catalyzed by boron trifluoride hydrate was carried out with benzyl, chlorobenzyl, alkylbenzyl, and alkoxybenzyl chlorides in boron trifluoride hydrate and hexane solutions. The relative rates of toluene to benzene were smaller than 1 in the benzylation with benzyl and chlorobenzyl chlorides, while they were larger than 1 with alkylbenzyl and alkoxybenzyl chlorides. Competitive benzylation catalyzed by boron trifluoride was also carried out in a nitromethane solution. The relative rates were reduced by from several to ten times in the former solutions as compared to the latter solution; the k_T/k_B value became smaller than 1 when the electrophile was such a very strongly electron-deficient reagent as the benzyl or chlorobenzyl cation. On the other hand, the k_T/k_B value was still larger than 1 when the electrophilicity was lower, as in the alkylbenzyl or alkoxybenzyl cation. The isomer distribution was insensitive to the nature of the solvents. The formation of the meta isomer was always only a small percentage. These results substantiate our previous conclusions obtained in the ethylation and isopropylation catalyzed by boron trifluoride hydrate.

Boron trifluoride-catalyzed ethylation with ethyl-2-^{14}C fluoride carried out in nonpolar organic solvents has indicated that an electrophile is not a donor:acceptor complex, but an ethyl cation.[1] Stock and Brown[2] suggested that, in aromatic substitution involving an ultimate powerful electrophile, the rate of toluene relative to benzene is 5/6 and that the orientation in the alkylation of toluene is 40% ortho, 40% meta, and 20% para isomer (statistical value). However, we found that the formation of the meta isomer of ethyltoluene or cymene is much lower than the statistical value, though the rate of toluene relative to benzene is smaller than 5/6, when the electrophile is such a very strongly electron-deficient reagent as the ethyl[3] or isopropyl[4] cation. The results do not agree with Brown's Selectivity Relationship.

Recently, some criticisms have been posed about such anomalous substrate selectivity that toluene is less reactive than benzene in spite of the electrophilic aromatic substitution. Carter *et al.*[5] carried out an ethylation of benzene and toluene with ethyl bromide under the influence of aluminium bromide in a hexane solution and concluded that the disproportionation and isomerization of products which occurred in the layer separation cause the reverse in the k_T/k_B value. Olah[6] suggested that, because of the secondary intermolecular rearrangement, the k_T/k_B value may apparently become smaller than 1 in the ethylation and the isopropylation, in which the *m*-isomer of ethyltoluene or isopropyltoluene usually is formed in a quantity of more than 20%.

In this work the benzylation catalyzed by boron trifluoride hydrate has been carried out with benzyl and substituted benzyl chlorides in order to substantiate our previous suggestion concerning the reaction mechanism of aromatic substitution involving the ultimate powerful electrophile.

Results and Discussion

Water dissolves small amounts of benzene and methylbenzenes.[7] Liquid boron trifluoride hydrate, which is formed when boron trifluoride is placed in contact with water, can also dissolve small amounts of benzene and methylbenzenes. When a boron trifluoride hydrate solution in which *o*-xylene and benzene have been dissolved is allowed to stand for many hours, both isomerization and disproportionation are observed to progress very slowly. When benzyl chloride is added to the boron trifluoride hydrate solution, dissolving the aromatics, the benzylation, accompanied by a little polymerization, occurs. The reaction is very rapid. The competitive benzylation of benzene and toluene with benzyl, *o*-, *m*-, *p*-chlorobenzyl, *p*-methyl-, *p*-ethyl-, *p*-isopropyl-, and *p*-methoxybenzyl chlorides was carried out in the boron trifluoride hydrate solution. The reaction proceeded in a homogeneous system. The data obtained are shown in Table 1. The rates of toluene relative to benzene, k_T/k_B, were smaller than 1 in the reactions with benzyl and chlorobenzyl chlorides, while they were larger than 1 in the reactions with *p*-alkyl- and *p*-alkoxybenzyl chlorides. No dibenzyltoluene was found. The benzylation catalyzed by boron trifluoride was also carried out in hexane. The data obtained are shown in Table 2. The results obtained were almost the same as those obtained in the boron trifluoride hydrate solution. Therefore, it appears that the catalyst in the hexane solution is not boron trifluoride itself, but boron trifluoride hydrate, as was suggested in previous works.[3,4] For comparison, a boron trifluoride-catalyzed benzylation was

TABLE 1. BORON TRIFLUORIDE HYDRATE-CATALYZED BENZYLATION IN BORON TRIFLUORIDE HYDRATE SOLUTIONS AT ROOM TEMPERATURE

R of $RC_6H_4CH_2Cl$	k_T/k_B	Isomer distribution (%)			$\frac{1}{2}o/p$
		o-	*m*-	*p*-	
o-Cl	0.5	46.5	16.1	37.4	0.62
m-Cl	0.8	47.2	15.5	37.3	0.63
p-Cl	0.5	46.8	6.1	47.1	0.50
H	0.9	43.6	6.1	50.3	0.43
p-CH_3	4.4	29.1	2.6	68.3	0.21
p-C_2H_5	5.6	28.1	2.9	69.0	0.20
p-*i*-C_3H_7	4.4	25.4	2.2	72.4	0.18
p-CH_3O	34	27.4	1.3	71.3	0.19

Table 2. Boron trifluoride hydrate-catalyzed benzylation in hexane at room temperature

R of $RC_6H_4CH_2Cl$	k_T/k_B	Isomer distribution (%) *o*-	*m*-	*p*-	$\frac{1}{2}o/p$
o-Cl[a)]	(0.7)	(42.2	16.0	41.8)	(0.53)
m-Cl	—	—	—	—	—
p-Cl	0.7	45.5	4.3	50.3	0.45
H	0.7	43.1	4.6	52.3	0.41
p-CH_3	4.4	24.4	2.1	73.4	0.17
p-C_2H_5	5.7	24.3	1.8	73.9	0.16
p-*i*-C_3H_7	3.1	21.3	1.8	76.9	0.14
p-CH_3O	23	28.4	3.8	67.8	0.21

a) The yield is very low.

Table 3. Boron trifluoride-catalyzed benzylation in nitromethane at room temperature

R of $RC_6H_4CH_2Cl$	k_T/k_B	Isomer distribution (%) *o*-	*m*-	*p*-	$\frac{1}{2}o/p$
o-Cl	2.8	38.2	15.8	46.0	0.42
m-Cl	3.5	37.8	10.2	52.0	0.36
p-Cl	2.8	44.6	7.4	48.0	0.46
H	3.7	40.5	6.5	53.0	0.38
p-CH_3	36	29.8	2.3	67.9	0.22
p-C_2H_5	38	27.6	2.7	69.6	0.20
p-*i*-C_3H_7	37	26.4	2.4	71.2	0.18
p-CH_3O	106	29.8	1.4	68.8	0.22

carried out in nitromethane. The results obtained were similar to those obtained by others,[8)] as is shown in Table 3. The finding that the formation of the *m*-isomer is only a small percentage in most of the reactions indicates that few thermodynamical side reactions (*i.e.*, isomerization and transalkylation) occur. The isomer distribution was almost independent of the nature of the solvent, while the k_T/k_B value was very sensitive to the reaction conditions.

Electrophile in Boron Trifluoride Hydrate-catalyzed Benzylation. The hydrates of $SnCl_2$, $SnCl_3$, $SnCl_4$, $ZnCl_2$, $FeCl_3$, $SbCl_3$, $SbCl_5$, $BiCl_2$, and $TiCl_4$ catalyze the benzylation of aromatics with benzyl chloride in aqueous media.[9)] Olah[10)] suggested that the investigated hydrates of metallic halides possess certain proton-acid catalytic activity and that the hydrolysis of benzyl chloride itself must proceed through a cation-type intermediate, capable under suitable conditions of effecting concurrent benzylation. The boron trifluoride hydrate is also a strong proton acid of a trifluorohydroxoboric or difluorodihydroxoboric acid type. The molar ratio of boron trifluoride to water in the boron trifluoride hydrate used for the benzylation is 0.77. In the solution there exists no free boron trifluoride which forms with benzyl chloride a polar donor:acceptor complex, $\overset{\delta+}{C_6H_5CH_2Cl}\cdot\overset{\delta-}{BF_3}$. The reaction of benzyl chloride with the boron trifluoride hydrate cannot give a donor:acceptor complex, since benzyl chloride is a much weaker donor than water. Therefore, in the boron trifluoride hydrate solution a benzyl cation-type intermediate is formed. Benzyl cation polymerizes when aromatics are not dissolved in the solution, but it becomes the electrophile of the benzylation in the presence of aromatics.

$$H_2O + BF_3 \rightleftharpoons H^+BF_3OH^-$$

$$H^+BF_3OH^- + C_6H_5CH_2Cl \longrightarrow C_6H_5CH_2{}^+BF_3OH^- + HCl$$

$$C_6H_5CH_2{}^+BF_3OH^- + ArH \longrightarrow C_6H_5CH_2Ar + H^+BF_3OH^-$$

The above presumption is also supported by the observations that an ethyl cation is the electrophile in the ethylation carried out with ethyl-1-^{13}C fluoride and ethyl-1,1-d_2 fluoride in the boron trifluoride hydrate solution.[11)]

Effect of Electrophilicity of Reagents on Selectivity. Olah, *et al.*[8)] concluded that intermolecular selectivity (rate ratio) is inversely related to the amount of polarization of the polar complex, while intramolecular selectivity (isomer distribution) is insensitive to the nature of the alkylating agent in the benzylation of benzene and toluene with benzyl and substituted benzyl halides in the presence of various Lewis acid catalysts. The explanation was made that the transition state can vary from a late one resembling an intermediate (σ complex) to an early one resembling the starting material (π complex), whereas the isomer distribution is related to the stability of the σ complex. The results obtained in this work showed effects similar to those found by Olah. The electrophile is the cation in the boron trifluoride hydrate-catalyzed benzylation, while it is the polar complex in the boron trifluoride-catalyzed benzylation. Since the electron deficiency of the former is much higher than that of the latter, the k_T/k_B values are reduced by as much as ten times in the boron trifluoride hydrate and hexane solutions as compared to the nitromethane solution. When the boron trifluoride-catalyzed benzylation was carried out with benzyl and chlorobenzyl chlorides in the latter solution, the k_T/k_B value was about 3. Consequently, the k_T/k_B value became smaller than 1 in the boron trifluoride hydrate and hexane solutions. On the other hand, the isomer distribution is less sensitive to the nature of the catalyst.

Rate-determining Step in the Boron Trifluoride Hydrate-catalyzed Benzylation. In the benzylation catalyzed by the boron trifluoride hydrate, the rupture of the C–Cl bond in benzyl or substituted benzyl chloride is complete before the reaction with the aromatics. The question arises whether or not an S_N1-type mechanism is applicable. If the rupture of the C–Cl bond determines the rate of the benzylation, the relative rate should always become 1, whether a substituted group of benzyl chloride is electron-attractive or electron-donative. The fact that the k_T/k_B values in the benzylation with *p*-alkyl- and *p*-alkoxybenzyl chlorides are from 4 to 34 indicates that the formation of *p*-alkyl- and *p*-alkoxybenzyl cations is not involved in the rate-determining step. On the other hand, the k_T/k_B values in the benzylation with chlorobenzyl chlorides are much smaller than 1. These values also suggest that the rate-determining step is not the rupture of the C–Cl bond in chlorobenzyl chlorides.

The benzylation proceeds in the homogeneous system, and few thermodynamical side reactions occur. However, since the reaction is very rapid, there are the possibilities that the reaction takes place at a point of entrance of benzyl or substituted benzyl chlorides into the boron trifluoride hydrate solution in which aromatics are dissolved and that the diffusion of aromatics in the solution determines the rate of the benzylation. If so, the k_T/k_B value should be nearly 1, but it may change from 0.5 to 34 depending on the electrophilicity of the substituted benzyl cations.

Consequently, the benzylation catalyzed by the boron trifluoride hydrate involves an electrophilic attack on aromatics by the benzyl or substituted benzyl cation. When the electron deficiency of the cation is very high, benzene is more reactive than toluene, but only a small percentage of the meta isomer of benzyltoluene is formed. This substantiates our previous suggestions[4] that the rate-determining transition state formed in the substitution of toluene closely resembles the oriented π complex, that the difference in rates between benzene and toluene is due primarily to the difference in the entropies of activation, which can be negative, since the difference in the activation energies between the two aromatics is very small, and that the isomerization of benzyltoluene is mainly determined by the stability of the intermediate (σ complex).

Experimental

Material. The benzene, toluene, *p*-methoxybenzyl chloride, and nitromethane were obtained from the Wako Pure Chemical Co. (Osaka, Japan). The benzyl chloride, chlorobenzyl chlorides, *p*-alkylbenzyl chlorides, and hexane were obtained from the Tokyo Kasei Co. (Tokyo, Japan). The boron trifluoride gas was obtained from the Hashimoto Kasei Co. (Osaka, Japan). They all were commercially available materials of the highest purity and were used without further purification.

Benzylation in Boron Trifluoride Hydrate Solution. *Preparation of a Boron Trifluoride Hydrate Solution Saturated with Aromatics*: Boron trifluoride gas was introduced into an ice-cooled and stirred mixture composed of 20 mol of distilled water, 1 mol of benzene, and 1 mol of toluene. The amount of boron trifluoride absorbed in the mixture was estimated by means of the flow speed of the boron trifluoride gas (6.2 l/min). The molar ratio of boron trifluoride to water in the mixture was 0.77. After the introduction of boron trifluoride gas had finished, the mixture was allowed to stand overnight and was then separated into two liquid-phase layers. The lower layer was the boron trifluoride hydrate solution saturated with benzene and toluene. It was a clear, colorless, viscous solution, and its specific gravity was 1.73 at 30 °C. Small amounts of aromatics dissolved in the boron trifluoride hydrate solution were extracted with hexane and analyzed by gas chromatography. About 5 mg of aromatics[11] were dissolved in 10 g of the boron trifluoride hydrate solution, the molar ratio of toluene to benzene was from 0.8 to 1.2, according to the preparative conditions.

Preparation of a Boron Trifluoride Hydrate Solution Saturated with Benzyl or Substituted Benzyl Chlorides: Boron trifluoride gas was absorbed into an ice-cooled and stirred mixture of 20 mol of water and 0.05 mol of benzyl chloride or substituted benzyl chloride. The reactivity of benzyl chloride varied greatly with the substituent group. Therefore, the molar ratio of boron trifluoride to water in a boron trifluoride hydrate solution in which benzyl chlorides were dissolved was changed in order to obtain such appropriate reaction conditions that less than 15% of the combined aromatics were alkylated and no side reactions proceeded. The amount of boron trifluoride gas blown into the mixture was estimated by means of the flow speed (6.2 l/min). The molar ratio of boron trifluoride to water was 0.20 for *o*- and *m*-chlorobenzyl chlorides, 0.10 for benzyl chloride, *p*-chloro-, *p*-ethyl-, *p*-isopropyl-, and *p*-methoxybenzyl chlorides, and 0.01 for *p*-methylbenzyl chloride. Benzyl or substituted benzyl chlorides do not polymerize in a boron trifluoride hydrate solution in which the ratio of boron trifluoride to water is small. Benzyl or substituted benzyl chlorides dissolved in a boron trifluoride hydrate solution were used for benzylation after filterings out the crystals of boric acid which were produced by the hydrolysis of boron trifluoride, and after separating out any excess benzyl or substituted benzyl chlorides. Gas-chromatographic analysis showed no isomerization of benzyl or substituted benzyl chlorides dissolved in the boron trifluoride hydrate solution.

Competitive Benzylation in Boron Trifluoride Hydrate Solution. From 10 to 80 g of boron trifluoride hydrate, in which benzyl chloride or substituted benzyl chlorides had been dissolved, were added to a glass beaker containing 20 g of a boron trifluoride hydrate solution saturated with benzene and toluene. The reaction mixture, which was a clear, colorless solution, was stirred at room temperature and then instantly quenched by adding 70 g of icewater. The organic layer was extracted with 1 ml of hexane, washed with water, and dried with calcium chloride. It was analyzed by gas chromatography. Benzylation proceeded for about 15% of the combined aromatics.

Competitive Benzylation in Hexane. Competitive benzylation was carried out by blowing boron trifluoride gas into a mixture of benzene, toluene, benzyl chloride, and hexane which had been saturated with water. The molar ratio of reactants was as follows; C_6H_6: $C_6H_5CH_3$: $C_6H_5CH_2Cl$: C_6H_{14}: $BF_3=5:5:3:30:2$. The flow speed of the boron trifluoride gas was 230 ml/min. The mixture was stirred at room temperature, it was quenched with water after 5 to 60 min, and then it was washed with water, dried with calcium chloride, and analyzed by gas chromatography.

Competitive Benzylation in Nitromethane. Competitive benzylation was carried out in a solution with the following molar ratio: $C_6H_6 : C_6H_5CH_3 : C_6H_5CH_2Cl : CH_3NO_2 : BF_3 = 5:5:3:30:2$. The flow speed of the boron trifluoride gas was 230 ml/min. After from 5 to 60 min, the reaction mixture was quenched with water, extracted with diethyl ether, and dried with calcium chloride. It was then analyzed by means of gas chromatography.

Gas-chromatographic Analysis. The reaction products were analyzed with a Hitachi 163-type gas chromatograph using a hydrogen flame-ionization detector and a 3380A Reporting Integrator of Hullet Packard. A glass capillary column(length, 30 m; i.d., 0.28 mm) coated with sillicon OV-101 was used at 180 °C for benzylated products, while one with Ucon 550X was used at 150 °C for the analysis of the isomer of *o*-chlorobenzyltoluene.

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