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Articles

A Process Scheme Involving Transalkylation Reactions To Prepare *o*-Bromophenol from Phenol

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Abstract:

The bromination of phenol to *o*-bromophenol was carried out by protecting the *para* position with a *tert*-butyl group. The latter group was subsequently transferred to toluene using aluminum chloride as a catalyst. The resulting mixture of *p*- and *m-tert*-butyltoluene could be converted back to *p-tert*-butylphenol by transalkylation of the former with phenol in the presence of Engelhard, F-24. Thus, a process scheme based on transalkylation reactions as the intermediate steps has been proposed to synthesize *o*-bromophenol from phenol via *p-tert*-butylphenol. The effect of reaction parameters on overall conversion to and selectivity with respect to the desired product was studied for the transalkylation reactions involved in the process.

1. Introduction

o-Halogenated phenols are important intermediates for the synthesis of catechol and its derivatives, which have diverse uses in the preparation of pharmaceuticals, agrochemical, flavors, antioxidants, and polymer inhibitors. However, the halogenation of phenols at room temperature invariably gives a mixture of *ortho* and *para* isomers, *para* isomers being the major product. Pearson et al.[1] have brominated phenols exclusively at the *ortho* position in the presence of *tert*-butylamine or triethylenediamine; however, the reaction was carried out at a very low temperature of about −70 °C. Hence, a general approach to obtain *o*-bromophenol in good yield is by an indirect procedure, involving blocking of the *para* position of phenol with a subsistent which can later be removed. Patai and Rapport[2] have summerized indirect procedures for obtaining *o*-halophenols, in which the *para* position is protected by carboxylic acid, sulfonic acid, and amino groups. However, as reported by Francis and Hill,[3] groups such as carboxylic acid and sulfonic acid are likely to be partially replaced by bromine during the bromination step. This problem can be circumvented by protecting the *para* position with a *tert*-butyl group, which is fairly stable under the conditions employed during bromination and can be transferred to another aromatic ring via a transalkylation reaction. Tashiro et al.[4] have reported the use of *tert*-butyl and benzyl groups as protecting groups in *ortho*-chlorination and -bromination of phenol. They have obtained *o*-bromophenol (OBP) in 82% yield by transalkylation of *o*-bromo-*p-tert*-butylphenol (OBPTBP) using benzene as an alkyl group acceptor and $AlCl_3-CH_3NO_2$ as a catalyst. This work was, therefore, carried out on similar lines to investigate the possibility of using toluene instead of benzene as an alkyl group acceptor and aluminum chloride as catalyst. The resulting mixture of *p*- and *m-tert*-butyltoluene (PTBT and MTBT) was used for obtaining *p-tert*-butylphenol (PTBP) by a transalkylation reaction with phenol in the presence of Engelhard, F-24. In this process, the amount of waste products is minimized, although the number of steps used in the process increases. Thus, a process scheme involving transalkylation reactions to prepare *o*-bromophenol from phenol via *p-tert*-butylphenol was developed, which consists of three reactions as shown in Figure 1.

2. Experimental Section

All the materials used were of technical grade. The clay catalyst Engelhard, F-24, was obtained from Engelhard, Corp. (Iselin, NJ). The experiments were carried out in a 0.5-L capacity glass reactor, provided with a six-blade turbine stirrer, four baffles, and a thermometer pocket. The reactor was placed in a constant-temperature bath.

2.1. Monobromination of PTBP. PTBP (2 mol/L) in 1,2-dichloroethane was taken in a reactor, and liquid bromine (2.1 mol/L) was added to it in 3 h by a dropping funnel. The reaction was carried out at 30 °C with continuous stirring. A slight excess of bromine was added to compensate for the loss due to vaporization. After complete addition of bromine, the reaction mixture was stirred for 1 h, and the product mixture was extracted with water to remove dissolved hydrogen bromide. The organic layer was dried over anhydrous sodium sulfate and solvent distilled to give OBPTBP in 98% yield.

2.2. Transalkylation of OBPTBP. Predetermined quantities of toluene, OBPTBP, and anhydrous aluminum chloride were taken in the reactor and stirred at the desired temperature. After the predetermined reaction period was over, the

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[1] Pearson, D. E.; Wysong, R. D.; Breder, C. V. J.; *J. Org. Chem.* **1967**, *32*, 2358−60.

[2] Patai, S.; Rapport, A. *The chemistry of functional groups*; Wiley: New York, 1983; Supplement D, Part 1, pp 522−32.

[3] Francis, A. W.; Hill, A. J. *J. Am. Chem. Soc.* **1924**, *46*, 2498−505.

[4] Tashiro M.; Watanabe, H.; Tsuge, O. *Org. Prep. Proced. Int.* **1974**, *6* (3), 107−15.

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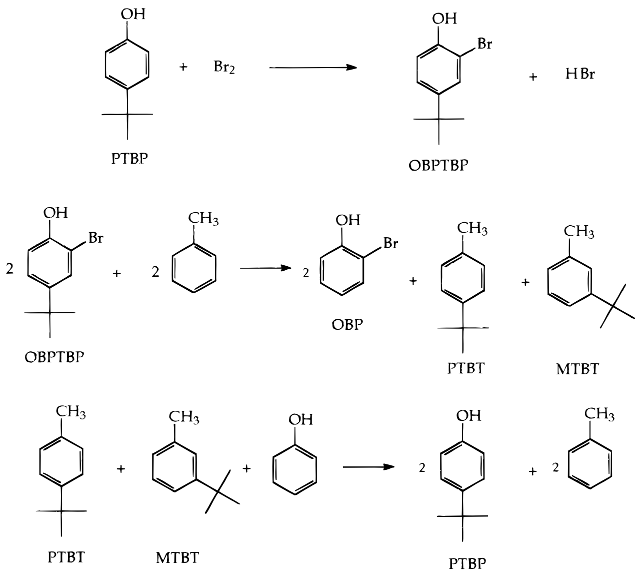

Figure 1. **Process scheme involving transalkylation reactions to synthesize *o*-bromophenol from phenol (PTBP = *p*-*tert*-butylphenol, OBPTBP = *o*-bromo-*p*-*tert*-butylphenol, OBP = *o*-bromophenol, PTBT = *p*-*tert*-butyltoluene, MTBT = *m*-*tert*-butyltoluene).**

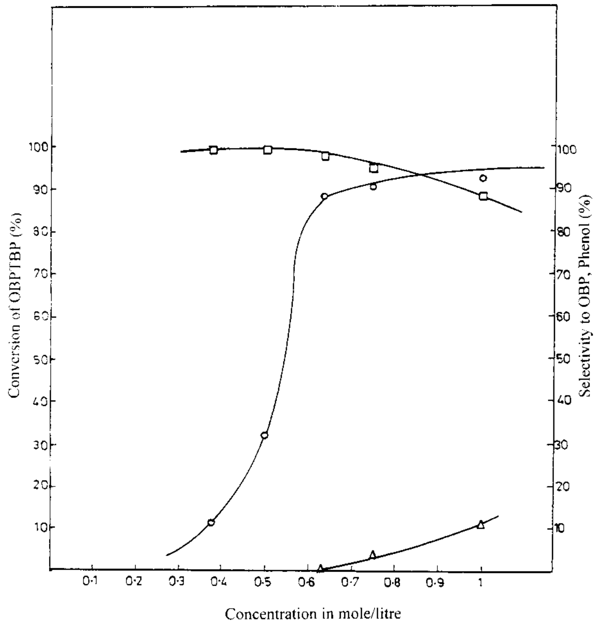

Figure 2. **Effect of aluminum chloride concentration on ○, conversion of OBPTBP; □, selectivity for OBP; △, selectivity for phenol (OBPTBP, 1.456 mol/L; temperature, 30 °C; reaction period, 3 h).**

product mixture was cooled to room temperature, and the reaction was quenched with 10% hydrochloric acid. The organic layer was separated and analysed. The mixture of phenols was isolated by extracting the product mixture with 10% aqueous sodium hydroxide solution and acidifying the extract with concentrated hydrochloric acid. The fractional distillation of the mixture of phenols under vacuum gave pure OBP. The mixture of PTBP and MTBT was separated from toluene by fractional distillation.

Table 1. **Effect of mole ratio of toluene to OBPTBP**[a]

no.	molar ratio of toluene OBPPTBP	conversion of OBPTBP (mol %)	selectivity to OBP (%)	conversion to OBP (mol %)
1	2:1	25	98	24.5
2	4.32:1	88	98	86.2
3	7:1	92	98	90.2
4	11:1	96	98	93.1

[a] Aluminum chloride, 0.626 mol/L; reaction temperature, 30 °C; reaction period, 3 h.

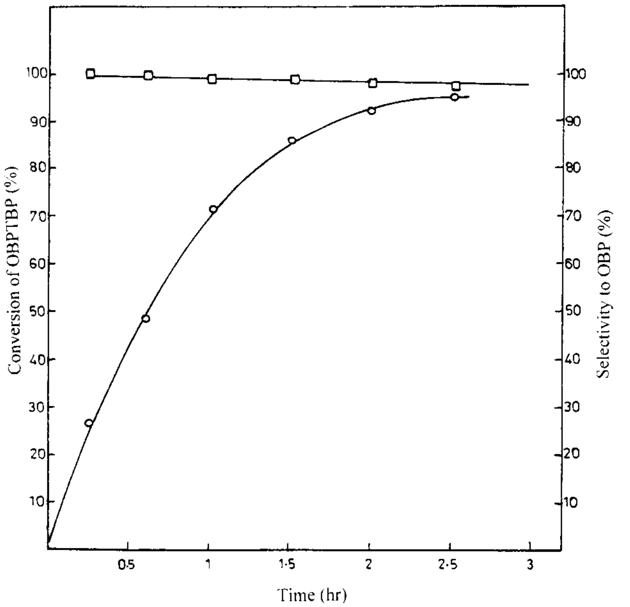

Figure 3. **Effect of reaction period on ○, conversion of OBPTBP; □, selectivity for OBP (OBPTBP, 0.728 mol/L; aluminum chloride, 0.626 mol/L; temperature, 30 °C).**

2.3. Transalkylation of the Mixture of PTBT and MTBT. Predetermined quantities of phenol, mixture of PTBT and MTBT, and Engelhard, F-24 were taken in the reactor and stirred at the desired temperature. Samples were withdrawn at regular intervals and analysed.

3. Analysis

The analysis of the reaction mixture was done by gas chromatography (Chemito 8510 gas chromatography, Toshniwal Instruments, Mumbai, India) using a 4-m stainless steel column packed with OV-17 (10%) on chromosorb WHP. However, in this column, the mixture of PTBT and MTBT was not separated and appeared as a single peak. Hence, to find the percentage composition of *tert*-butyltoluenes, a 4-m stainless steel column packed with Betone-34 (5%) on chromosorb WHP was used.

4. Results and Discussion

4.1. Transalkylation of OBPTBP. *4.1.1. Effect of Aluminum Chloride Concentration.* At a lower catalyst concentration of 0.5 mol/L of aluminum chloride, the conversion of OBPTBP was only 32%, and the selectivity for OBP was 99% in 3 h (Figure 2). With an increase in the concentration of the catalyst, the conversion increased sharply, and at a catalyst concentration of 0.626 mol/L the conversion was 88%, with selectivity for OBP remaining almost constant. With a further increase in the concentration

Table 2. **Effect of period of reaction**[a]

no.	reaction period (h)	conversion of OBPTBP (mol %)	selectivity to OBP (%)	conversion to OBP (mol %)	rate (K h^{-1})
1	0.25	26.8	99	26.6	1.25
2	0.5	48.0	99	47.5	1.31
3	1.0	71.3	98	69.9	1.25
4	1.5	86.3	98	84.6	1.32
5	2.0	92.8	98	90.9	1.31
6	2.5	95.4	98	93.5	1.23

[a] OBPTBP, 0.728 mol/L; aluminum chloride, 0.626 mol/L; reaction temperature, 30 °C.

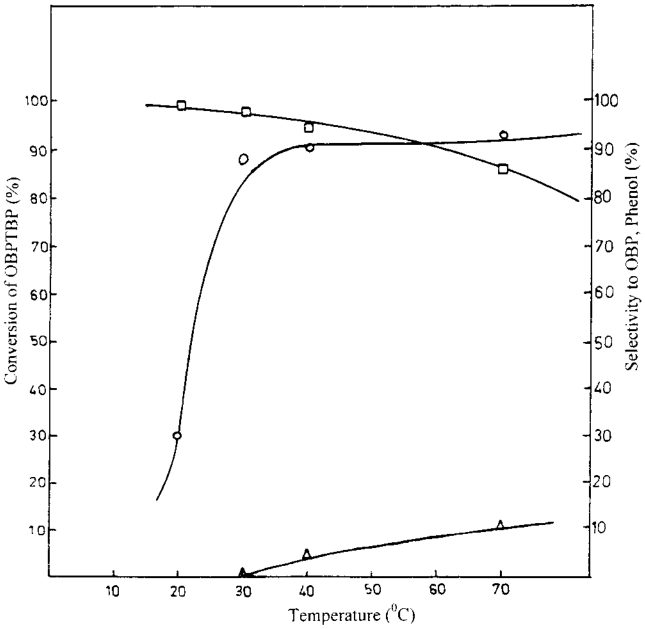

Figure 4. **Effect of temperature on ○, conversion of OBPTBP; □, selectivity for OBP; △, selectivity for phenol (OBPTBP, 1.456 mol/L, aluminum chloride, 0.626 mol/L; reaction period, 3 h).**

Table 3. **Change in composition of mixture of *tert*-butyltoluenes with time during transalkylation of OBPTBP**[a]

no.	time (min)	MTBT (%)	PTBT (%)
1	10	30	70
2	15	53	47
3	30	65	35
4	60	64	36
5	120	64	36

[a] OBPPTBP, 0.728 mol/L; aluminum chloride, 0.628 mol/L; reaction temperature, 30 °C.

Table 4. **Effect of Engelhard, F-24 loading**[a]

no.	catalyst loading (% w/v)	conversion of *tert*-butyltoluenes (mol %)	selectivity to PTBP (%)	conversion to PTBP (mol %)
1	2	37	99	36.6
2	5	74	94	69.7
3	10	80	92	73.6
4	12	83	90	74.7
5	15	85	85	72.2

[a] *tert*-Butyltoluenes, 1.89 mol/L; reaction temperature, 170 °C; reaction period, 3 h.

Table 5. **Effect of reaction temperature**[a]

no.	reaction temperature (°C)	conversion of *tert*-butyltoluenes (mol %)	selectivity to PTBP (%)	conversion to PTBP (mol %)
1	120	10	99	9.9
2	130	32	98	31.4
3	150	55	95	52.2
4	170	83	90	74.7

[a] *tert*-Butyltoluenes, 1.89 mol/L; Engelhard, F-24, 12% w/v; reaction period, 3 h.

of catalyst, although conversion increased, selectivity for OBP dropped and phenol was obtained as a byproduct due to debromination of OBP.

4.1.2. Effect of Mole Ratio of Toluene to OBPTBP. As transalkylation reactions are reversible, it is necessary to take one of the components in excess to achieve higher conversion. Hence, the effect of the mole ratio of toluene to OBPTBP was studied (Table 1). At the mole ratio of 2:1 toluene to OBPTBP, the conversion was only 25%, with 98% selectivity for OBP in 3 h. As the mole ratio was increased, the conversion of OBPTBP increased, while the selectivity remained effectively constant. At a mole ratio of 11:1, when the concentration of OBPTBP was 0.728 mol/L, the conversion of OBPTBP was 96%, with 98% selectivity for OBP.

4.1.3. Effect of Period of Reaction. Kinetic data were obtained by varying the period of reaction from 0.5 to 3 h using 0.728 mol/L of OPPTBP and 0.626 mol/L of aluminum chloride at 30 °C (Figure 3). The values of selectivity for OBP remained almost constant at various levels of conversions. As toluene was taken in excess, although transalkylation reactions are reversible, the kinetic data correlate with an irreversible pseudo-first-order reaction with respect to OBPTBP. The values of specific reaction rate for the disappearance of OBPTBP, as estimated from the integrated form of the first-order rate expression, were found to be essentially constant (Table 2).

4.1.4. Effect of Temperature. The temperature was varied in the range of 20−70 °C (Figure 4). At 20 °C, the rate of reaction was very low, and only 30% conversion of OBPTBP was obtained with 99% selectivity to OBP in 3 h. When the temperature was increased to 30 °C, there was an improvement in the rate of reaction, and the conversion increased to 88% while the selectivity remained almost the same. With a further increase in the temperature, although the conversion increased, the selectivity for OBP decreased and more of phenol formed. The apparent activation energy calculated from the Arrhenius plot was found to be 41.8 kcal/mol.

The change in mole composition of the mixture of PTBT and MTBT with time was studied (Table 3). It was observed that initially a larger amount of PTBT was obtained. After 0.5 h, the mixture consisted of about 36% of PTBT and 64% of MTBT. This distribution of isomers remained constant and was found to be the same as that reported by Olah et

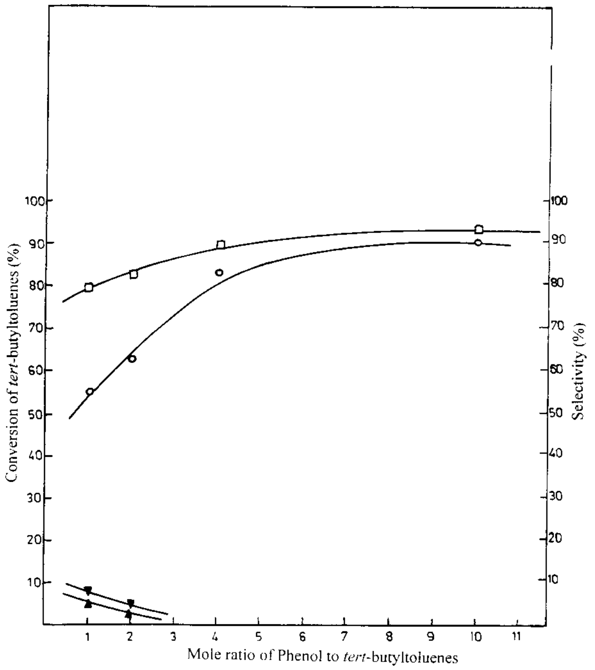

Figure 5. **Effect of mole ratio of phenol to *tert*-butyltoluene on ○, conversion of *tert*-butyltoluenes; □, selectivity for PTBP; ▼, selectivity for *o-tert*-butylphenol; ▲, selectivity for 2,4-di-*tert*-butylphenol (Engelhard, F-24, 12% w/v; temperature, 170 °C; reaction period, 3 h).**

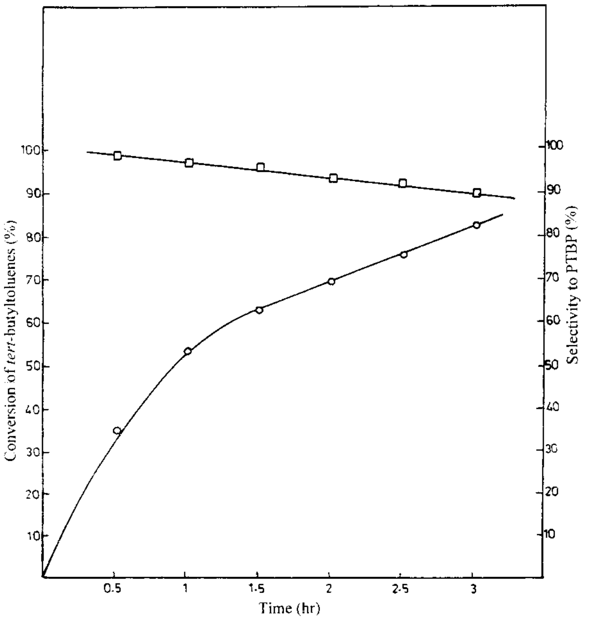

Figure 6. **Effect of reaction period on ○, conversion of *tert*-butyltoluenes; □, selectivity for PTBP (*tert*-butyltoluenes, 1.89 mol/L; Engelhard, F-24, 12% w/v; temperature, 170 °C).**

al.[5] when they studied isomerisation of *tert*-butyltoluenes in the presence of aluminum chloride.

4.2. Transalkylation of the Mixture of PTBT and MTBT. *4.2.1. Effect of Speed of Agitation.* There was no effect of the speed of agitation on the rate of reaction in the range 800−1500 rpm. This showed that there was no external mass transfer limitation in the range of stirrer speeds employed. For subsequent runs, the agitator speed was maintained at 1000 rpm.

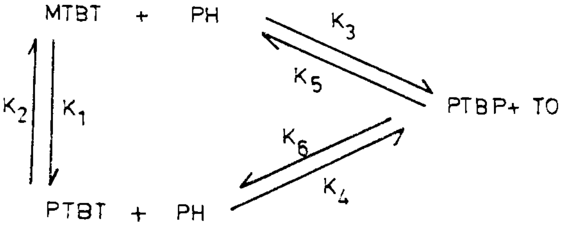

Figure 7. **Network of the reaction (PH = phenol, TO = toluene).**

Table 6. **Values of apparent rate constants[a]**

k_1	2.46×10^{-3}
k_2	2.16×10^{-2}
k_3	1.44×10^{-3}
k_4	4.04×10^{-3}
k_5	2.10×10^{-9}
k_6	3.30×10^{-3}

[a] *tert*-Butyltoluenes, 1.89 mol/L; Engelhard, F-24, 12% w/v; reaction temperature 170 °C.

4.2.2. Effect of Catalyst Loading. The effect of loading of acid-activated clay, Engelhard, F-24, expressed as % w/v of reaction mixture, was studied between 2 and 15% (Table 4). At a lower catalyst loading of 2% w/v, only 37% conversion of *tert*-butyltoluenes was obtained, with 99% selectivity for PTBP. As the catalyst loading was increased to 12% w/v, the conversion increased to 83%. However, selectivity for PTBP decreased to 90%.

4.2.3. Effect of Temperature. The effect of temperature was studied from 120 to 170 °C (Table 5). When temperature was increased from 120 to 170 °C, the conversion of *tert*-butyltoluene increased from 10% to 83%; however, the selectivity to PTBP decreased from 99% to 90%.

4.2.4. Effect of Mole Ratio of Phenol to tert-Butyltoluenes. The mole ratio of phenol to *tert*-butyltoluene was found to have a significant effect on conversion and selectivity (Figure 5). At a lower mole ratio of 1:1 phenol to *tert*-butyltoluenes, both the conversion of *tert*-butyltoluene and the selectivity for PTBP were poor, and *o-tert*-butylphenol and 2,4-di-*tert*-butylphenol were obtained as side products. As the mole ratio of phenol to *tert*-butyltoluenes increased to 4:1, the conversion increased, with a simultaneous increase in the selectivity with respect to PTBP.

4.2.5. Effect of Period of Reaction. The effect of period of reaction on the overall conversion of *tert*-butyltoluenes and on selectivity with respect to PTBP was studied (Figure 6). Also, the change in composition of the mixture of *tert*-butyltoluenes with time was studied, and a kinetic model was developed based on the reaction network shown in Figure 7. The rates of formation of various species can be written as

$$\frac{d[\mathrm{PTBT}]}{dt} = K_1[\mathrm{MTBT}] + K_6[\mathrm{PTBP}][\mathrm{TO}] - K_4[\mathrm{PTBT}][\mathrm{PH}] - K_2[\mathrm{PTBT}] \quad (1)$$

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(5) Olah, G. A.; Meyer, M. w.; Overchuk, N. A. *J. Org. Chem.* **1964**, *29*, 2310−2.

$$\frac{d[\mathrm{MTBT}]}{dt} = K_2[\mathrm{PTBT}] + K_5[\mathrm{PTBP}][\mathrm{TO}] - K_3[\mathrm{MTBT}][\mathrm{PH}] - K_1[\mathrm{MTBT}] \quad (2)$$

$$\frac{d[\mathrm{PTBP}]}{dt} = K_3[\mathrm{MTBT}][\mathrm{PH}] + K_4[\mathrm{PTBT}][\mathrm{PH}] - (K_5 + K_6)[\mathrm{PTBP}][\mathrm{TO}] \quad (3)$$

The three simultaneous differential equations (eqs 1−3) were solved numerically by the fourth-order Runge−Kutta method. The apparent rate constants, viz. k_1, k_2, k_3, k_4, k_5, and k_6, were evaluated by minimizing the difference between the experimental concentration and the concentration predicated by the model using the method of least squares (Table 6). The Resenbrock method of rotating coordinates was employed for the purpose of optimization. A good agreement was found between the experimental and predicated concentration profiles (Figure 8).

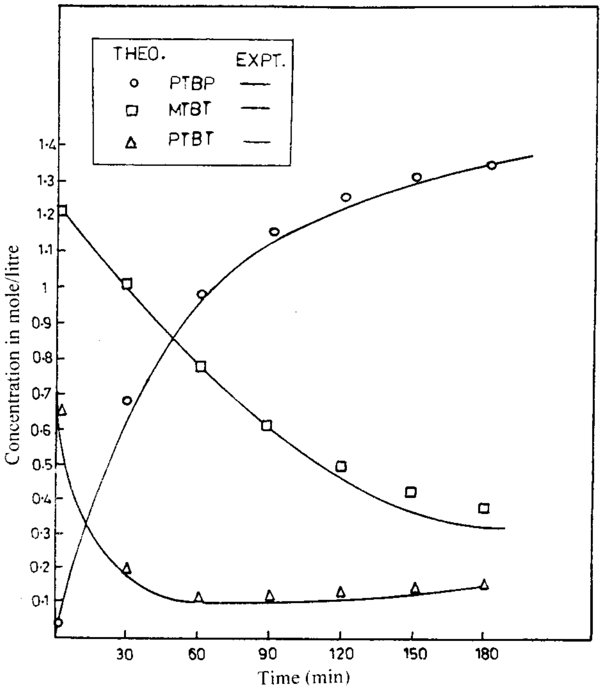

Figure 8. **Comparison between theoretical and experimental concentration profiles of different species.**

Conclusions

o-Bromophenol can be successfully synthesized from phenol using a *tert*-butyl group as a positional protecting group. The process involves bromination of PTBP to give OBPTBP, which on transalkylation reaction with toluene at 30 °C in the presence of aluminum chloride gave OBP and a mixture of PTBT and MTBT. The reaction was pseudo-first-order with respect to OBPTBP, and the activation energy of the reaction was 41.8 kcal mol^{-1}. The coproduct of this reaction, viz. the mixture of *tert*-butyltoluenes, on transalkylation reaction with phenol in the presence of Engelhard, F-24 at 170 °C gave PTBP, which can be recycled, although with low efficiencies based on phenol. The kinetic model based on the suggested reaction networks fits the exprimental data well.

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NOMENCLATURE

PTBP = *p*-*tert*-butylphenol
OBPTBP = *o*-bromo-*p*-*tert*-butylphenol
OBP = *o*-bromophenol
PTBT = *p*-*tert*-butyltoluene
MTBT = *m*-*tert*-butyltoluene
PH = phenol
TO = toluene

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