The *O*-Alkylation of Phenols by Esters. II. The Steric Hindrance and Electronic Effect in the *O*-Alkylation of Phenol by Esters[1]

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The steric hindrance in the *O*-alkylation of PhOK by alkyl acetate (PhOK+AcOR→PhOR+AcOK) was examined by means of competitive reactions. As a result, the following sequence of the reactivities of alkyl acetates was obtained: $CH_3 \gg C_2H_5 > n\text{-}C_3H_7 \gtrsim n\text{-}C_4H_9 > s\text{-}C_4H_9 > i\text{-}C_3H_7 \gtrsim i\text{-}C_4H_9 > t\text{-}C_4H_9$ and $n\text{-}C_4H_9 > n\text{-}C_5H_{11} > i\text{-}C_5H_{11}$. The electronic effect in the *O*-alkylation was also examined by means of the competitive reaction of *p*-substituted (CH_3 or CH_3O) methyl benzoate and methyl benzoate with PhOK. The reactivity decreases in the following order: $C_6H_5COOMe > p\text{-}CH_3C_6H_4COOMe > p\text{-}CH_3OC_6H_4COOMe$. Therefore, it was concluded that the rate-determining step is the attack of the phenoxide anion on the carbon atom of the methyl group.

There have been few reports on the *O*-alkylation of phenols by alkyl alkanoates except by alkyl oxalate and methyl trichloroacetate.[2,3] On the other hand, dialkyl sulfates and *p*-toluenesulfonic esters, which are the esters of strong acids, are known as powerful *O*-alkylating agents of phenols. The present authors have previously reported[1] that alkali phenoxides react with alkyl alkanoates at high temperatures to give alkyl phenyl ether. For example, alkali salts of phenols (RC_6H_4OH; where R is H, *o*-CH_3, *m*-CH_3, *p*-CH_3, *o*-Cl, or *p*-Cl) react with the methyl ester of acetic acid, acrylic acid, or methacrylic acid to give the corresponding anisoles ($RC_6H_4OCH_3$). The runs using alkali phenoxides with ortho-substituent or those with electron-attracting substituents gave the corresponding anisoles in lower yields. In this paper, the effects of the alkyl and the acyl components in alkyl alkanoates on the *O*-alkylation were examined from the standpoint of the steric hindrance and the electronic effect.

Results and Discussion

Steric Hindrance. The reactions of potassium phenoxide with nine alkyl acetates were carried out. The results are summarized in Table 1.

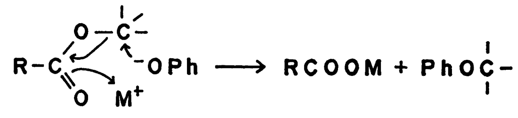
Table 1. Yields of alkyl phenyl ethers[a)]

R	Yield of ROPh (%)	
	200 °C[b)]	250 °C[b)]
CH_3	75.3	78.7
C_2H_5	42.1	56.6
$n\text{-}C_3H_7$	—	55.0
$i\text{-}C_3H_7$	4.8	35.6
$n\text{-}C_4H_9$	33.5	56.1
$i\text{-}C_4H_9$	3.3	18.9
$s\text{-}C_4H_9$	13.9	20.0
$t\text{-}C_4H_9$[c)]	—	12.3
$n\text{-}C_5H_{11}$	17.1	37.9
$i\text{-}C_5H_{11}$	11.8	39.2

a) The reaction was carried out by using an excess of alkyl acetate (AcOR 0.5 mol and PhOK 0.05 mol). b) Reaction temp (Reaction time, 2 h). c) Many by-products were detected in the reaction mixture by gas chromatography.

In these esters, ethyl, propyl, and butyl acetates gave alkyl phenyl ethers in nearly equal yields. Branched alkyl acetates gave the ethers in lower yields.

In the previous paper,[1] the mechanism shown in Scheme 1 was suggested for the *O*-alkylation of alkali phenoxide by ester. According to this mechanism, not only the bulky alkyl component, but also the long-chain alkyl component, in alkyl acetate would hinder the attack of the phenoxide anion. However, we observed no great difference in yields when ethyl, propyl, and butyl acetates were used.



Scheme 1.

One method of evaluating the reactivity of each acetate towards potassium phenoxide is to compare the reaction rate constant in each reaction. However, there are few solvents which have high boiling points and which dissolve potassium phenoxide. Although potassium phenoxide is soluble in some aprotic polar solvents, such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and hexamethyl phosphoric triamide (HMPA), the rate of the disappearance of the ester (methyl benzoate) in the initial period was abnormally great when the reaction was carried out at high temperatures in these solvents. This phenomenon must result from the side reactions: that is, the hydrolysis of the ester by the water contained in the solvents (it is difficult to remove the water completely from such solvents) and the decomposition of DMF into carbon monoxide and dimethylamine in the presence of the base (PhOK).[4] The latter product further reacts with the ester to produce undesirable products.

Competitive reactions were used to compare the reactivity of each acetate to potassium phenoxide. The merit of this method is that we can carry out the reactions of several kinds of alkyl acetates with potassium phenoxide under the same conditions.

The competitive reactions were carried out by heating potassium phenoxide with a mixture of three alkyl acetates, and then the three alkyl phenyl ethers formed were determined by gas chromatography. The results are shown in Table 2. As has already been mentioned,

TABLE 2. COMPETITIVE REACTIONS OF ALKYL ACETATES WITH POTASSIUM PHENOXIDE[a]

Components of the mixture of esters[b]	i-C_3H_7OAc+ n-C_4H_9OAc+ s-C_4H_9OAc	C_2H_5OAc+ n-C_4H_9OAc+ i-C_4H_9OAc	C_2H_5OAc+ n-C_3H_7OAc+ n-C_4H_9OAc	C_2H_5OAc+ i-C_3H_7OAc+ n-C_4H_9OAc	CH_3OAc+ n-C_3H_7OAc+ n-C_4H_9OAc
AcOR, R=	Yields of alkyl phenyl ethers (ROPh), (%)				
CH_3	—	—	—	—	60.4
C_2H_5	—	53.0	28.1	38.3	—
n-C_3H_7	—	—	12.3	—	4.9
i-C_3H_7	1.7	—	—	7.4	—
n-C_4H_9	43.3	15.1	11.7	13.3	3.4
i-C_4H_9	—	2.6	—	—	—
s-C_4H_9	5.9	—	—	—	—
Total yields (%)	50.9	70.7	52.1	59.0	68.7

a) PhOK, 0.05 mol; reaction temp, 250 °C; reaction time, 2 h. b) Every mixture contains 0.15 mol portions of three esters.

the phenoxide anion would attack the less hindered carbon atom adjacent to the ether oxygen. Therefore, the ester with a longer-chain alkoxyl group will give an alkyl phenyl ether in a lower yield. Thus, the reactivities of the esters may be supposed to decrease in the following order: $CH_3OAc > C_2H_5OAc > n\text{-}C_3H_7OAc > n\text{-}C_4H_9OAc$. The branched alkyl acetate will give the alkyl phenyl ether in a yield lower than the normal alkyl acetate. From Table 2, the following sequence of the reactivities was obtained for the series of acetates: $n\text{-}C_4H_9 \gg s\text{-}C_4H_9 > i\text{-}C_3H_7$; $C_2H_5 > n\text{-}C_4H_9 > i\text{-}C_3H_7$; $C_2H_5 > n\text{-}C_4H_9 \gg i\text{-}C_4H_9$; $CH_3 \gg n\text{-}C_3H_7 > n\text{-}C_4H_9$; $C_2H_5 > n\text{-}C_3H_7 > n\text{-}C_4H_9$. It is preferable to use a mixture containing all the alkyl acetates in the competitive reaction, but it was difficult to determine each alkyl phenyl ether in the mixture by gas chromatography. The ratio of the yields in the same reaction will not be exactly equal to the ratio of the reactivities because the reaction rate is also dependent on the concentration of the ester. Under the present experimental conditions, the variation in the concentration of the ester can not be neglected when the yield of the alkyl phenyl ether is appreciably high. If a mixture containing excess amounts of esters is used to avoid the variation in the concentration during the reaction, the accurate determination of the products will become difficult. On the basis of the data shown in Tables 1 and 2, though, a reasonable order of the reactivities of alkyl acetates may be as follows: $CH_3 \gg C_2H_5 > n\text{-}C_3H_7 \gtrsim n\text{-}C_4H_9 > s\text{-}C_4H_9 \gtrsim i\text{-}C_3H_7 \gtrsim i\text{-}C_4H_9 > t\text{-}C_4H_9$ and $n\text{-}C_4H_9 > n\text{-}C_5H_{11} > i\text{-}C_5H_{11}$. Although the electronic effect, of course, influences the reactivity of the alkyl group, the reactivity might be controlled mainly by the steric hindrance.

It was reported previously[1] that ortho-substituted alkali phenoxides gave the corresponding ethers in lower yields. For example, potassium *p*- and *m*-methylphenoxide react with methyl methacrylate at 200 °C to afford anisole in 84.5 and 74.8% yields respectively. On the contrary, potassium *o*-methylphenoxide gave *o*-methylanisole in a 29.4% yield under the same conditions. Similarly, potassium *o*-chorophenoxide gave *o*-chloroanisole in a 13.9% yield, although potassium *p*-chlorophenoxide gave *p*-chloroanisole in a 48.9% yield. In Table 2, there are no examples of reactions using ortho-substituted phenoxide. The steric hindrance may also be caused by the interaction between the hydrogen atom on the ortho position of phenoxide and that of the alkoxyl group. In methyl acetate this interaction may be small, but the interaction will become important in ethyl and higher alkyl acetates. In fact, there was a great difference in the reactivity between methyl acetate and ethyl acetate, as is shown in Tables 1 and 2.

The steric hindrance of the acyl group was also examined; the results are summarized in Table 3. At a low temperature (150 °C), methyl pivalate and methyl decanoate gave anisole in lower yields than did the other esters. The decrease in the yield is attributable in part to the steric hindrance of the bulky group and the long chain.

TABLE 3. RELATIONSHIP BETWEEN THE YIELD OF ANISOLE AND THE ACID COMPONENT OF THE METHYL ESTER[a]

Ester RCOOMe	pK_a of RCOOH (25 °C)[a]	Yields of anisole (%)		
		150 °C	200 °C	250 °C[c]
$(CH_3)_3CCOOMe$	5.03[d]	13.4	—	—
$CH_3(CH_2)_8COOMe$	4.89	4.0	73.4[e]	—
CH_3CH_2COOMe	4.87	—	88.0	—
CH_3COOMe	4.76	54.5	79.2	—
$PhCH_2COOMe$	4.31	83.2	91.4	—
$PhCOOMe$	4.20	83.8	—	99.6

a) PhOK, 0.05 mol; ester/PhOK (mol/mol) = 10.
b) "Kagaku Binran, Kisohen II," Maruzen (1966); "Handbook of Tables for Organic Compound Identification," The Chemical Rubber Co. (1967). c) Reaction temp (reaction time, 5 h). d) At 18 °C.
e) Ester/PhOK = 8.8.

The Electronic Effect of the Acyl Group on the Reactivity. The electronic effect of the acyl group in alkyl alkanoate was also examined; the results are shown in Table 3. However, it is difficult to isolate only the electronic effect from the results shown in Table 3.

King reported[5] that methyl benzoate is a good *O*-alkylating agents (see also Table 3). Therefore, the electronic effect was investigated by using methyl *p*-substituted benzoate. A mixture of methyl *p*-substituted benzoate, methyl benzoate, potassium phenoxide, and cyclohexane (a heat medium) was heated in an autoclave, and the residual methyl *p*-substituted benzoate and methyl benzoate and the anisole formed from this

Table 4. Competitive reactions of *p*-substituted methyl benzoate and methyl benzoate with potassium phenoxide[a)]

Components of the mixture $xC_6H_5OK+yC_6H_5COOMe$ $+zp\text{-}RC_6H_4COOMe$ R;	$x:y:z$	Reaction time (h)	Yields of anisole (%) from C_6H_5COOMe (I)	Yields of anisole (%) from $p\text{-}RC_6H_4COOMe$ (II)	Total yield	Ratio $\frac{(I)}{(I)+(II)}$
CH_3[b)]	1 : 2.95 : 2.95	6	52.6	38.9	91.5	0.575
CH_3	1 : 1.01 : 1.01	9	51.7	48.2	99.9	0.518
CH_3	1 : 1.00 : 1.00	1	47.8	39.6	87.4	0.547
CH_3O[c)]	1 : 3.38 : 3.35	6	66.9	17.4	84.3	0.794
CH_3O	1 : 0.99 : 0.99	0.5	41.4	24.3	65.7	0.630

a) C_6H_5OK, 0.1 mol; reaction temp, 250 °C. b) $\sigma_p=-0.17$. c) $\sigma_p=-0.27$.

reaction were determined by gas chromatography. The results are shown in Table 4. As the steric hindrance of the *p*-substituents can be disregarded, the inductive effect and the resonance effect of these groups must become important in this reaction. Benzoic acid is the strongest acid, and *p*-anisic acid is the weakest one, of the three (the pK_a values of the acids at 25 °C are as follows: benzoic acid, 4.21; toluic acid, 4.37; *p*-anisic acid, 4.49[6)]). The electron-donating group on the para-position may increase both the electron densities on the oxygen atom of the carbonyl group (>C=O) and on the carbon atom of the methyl group ($-COOCH_3$). If the rate-determining step of this reaction is the nucleophilic attack of the phenoxide anion on the carbon atom of the methyl group, the electron-donating group may retard the attack of the phenoxide anion. On the contrary, if the rate-determining step is the activation of the phenoxide anion (although the oxygen atom of potassium phenoxide has an anionic character, it is neutralized by the potassium cation), the electron-donating group is advantageous for the *O*-alkylating reaction because the potassium cation may be neutralized to a greater extent by the oxygen atom of the carbonyl group and a more active phenoxide anion may be formed.

The molar ratios (potassium phenoxide: methyl benzoate: methyl *p*-substituted benzoate) and the reaction time were varied, and the yields of anisole from methyl benzoate and methyl *p*-substituted benzoate and its ratio were calculated. From the results listed in Table 4, the following facts became clear. The reactivities of both methyl toluate and anisate are lower than that of methyl benzoate, and the reactivity of methyl anisate is lower than that of methyl toluate. Therefore, the results lead to the conclusion that the attack of the phenoxide anion on the carbon atom adjacent to the ether linkage is more important than the formation of the active phenoxide anion.

The competitive reaction of methyl *p*-nitrobenzoate and methyl benzoate with potassium phenoxide was also carried out at 200 °C for 5 h and at 170 °C for 9 h. Under the former conditions, the yield of anisole was 15.2 and 83.6% of the methyl benzoate was recovered. On the contrary, only 8.6% of the methyl *p*-nitrobenzoate was recovered, while 91.4% of the methyl *p*-nitrobenzoate was consumed to produce unidentified by-products. In this case, a side reaction, which has no relation with the *O*-alkylation, most likely occurred.

Experimental

Competitive Reactions of Alkyl Acetates with Potassium Phenoxide. Because the experiments of other competitive reactions were carried out similarly, only one example will be given in detail.

An equimolar mixture (0.15 mol each) of methyl acetate, propyl acetate, and butyl acetate, and 0.05 mol of potassium phenoxide was placed in a 300-ml autoclave equipped with an electromagnetic stirrer. The reaction mixture was then heated at 250 °C for 2 h. It takes about 20 min to raise the temperature to 250 °C. After cooling, the reaction mixture was poured into water and the alkyl phenyl ether was extracted with ether (about 100 ml). To the ethereal solution, 0.05 mol of *N,N*-dimethylaniline (6.060 g) was then added as an internal standard compound and the anisole, propyl phenyl ether, and butyl phenyl ether were determined by gas chromatography (internal standard method; column, PEG 20M; temp, 200 °C).

Competitive Reactions of p-*Substitued Methyl Benzoate and Methyl Benzoate with Potassium Phenoxide.* To an equimolar mixture of methyl benzoate and methyl *p*-substituted benzoate, potassium phenoxide was added, after which the mixture was heated at 250 °C. After cooling, the anisole and the benzoates were extracted with ether (100 ml) and the molar ratios of anisole/methyl benzoate and methyl *p*-substituted benzoate/methyl benzoate were obtained by gas chromatography (column, PEG 20M; temp, 200 °C). The mole number of the anisole formed in this reaction must be equal to the sum of the mole numbers of the methyl benzoate and methyl *p*-substituted benzoate consumed in this reaction, because no product other than anisole was detected in the gas chromatogram. On the basis of this fact, the yields of anisole from methyl benzoate and from methyl *p*-substituted benzoate were calculated.

Identification of Alkyl Phenyl Ethers. Authentic alkyl phenyl ethers were prepared by Williamson ether synthesis,[7)] but *t*-butyl phenyl ether was prepared according to the directions described in "Organic Syntheses" (Vol. 45, p. 89). These ethers were identified by elementary analysis, NMR, and gas chromatography. The retention times of the alkyl phenyl ethers formed in this reaction were compared with those of authentic ethers. The two retention times were agreed within 2 s (the retention times of these ethers were from 124 s, CH_3OPh, to 333 s, *i*-$C_5H_{11}OPh$; column, PEG 20M, 30%; temp, 200 °C). Four ethers obtained from the reactions of potassium phenoxide and alkyl acetates (propyl, butyl, isobutyl, and *s*-butyl acetates) were isolated by gas chromatography and were identified by NMR (solvent, CCl_4).

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