

The importance of hydrogen bonding  
in the alkylation of phenols

by

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To my father

without whose encouragement,

I would not have entered graduate studies

nor completed this research work.

## Abstract

Hydrogen bond assisted alkylation of phenols is compared with the classical base assisted reactions. The influence of solvents on the fluoride assisted reactions is discussed, with emphasis on the localization of hydrogen bond charge density. Polar aprotic solvents such as DMF favour O-alkylation, and nonpolar aprotic solvents such as toluene favour C-alkylation of phenol. For more reactive and soluble fluorides, such as tetrabutylammonium fluoride, the polar aprotic solvent favours O-alkylation and nonpolar aprotic solvent favours fluorination. Freeze-dried potassium fluoride is a better catalytic agent in hydrogen bond assisted alkylation reactions of phenol than the oven-dried fluoride. The presence of water in the alkylation reactions reduces the expected yield drastically. The tolerance of the reaction to water has also been studied. The use of a phase transfer catalyst such as tetrabutylammonium bromide in the alkylation reactions of phenol in the presence of potassium fluoride is very effective under anhydrous conditions. Sterically hindered phenols such as 2,6-ditertiarybutyl-4-methyl phenol could not be alkylated even by using the more reactive fluorides, such as tetrabutylammonium fluoride in either polar or nonpolar aprotic solvents. Attempts were also made to alkylate phenols in the presence of triphenylphosphine oxide.

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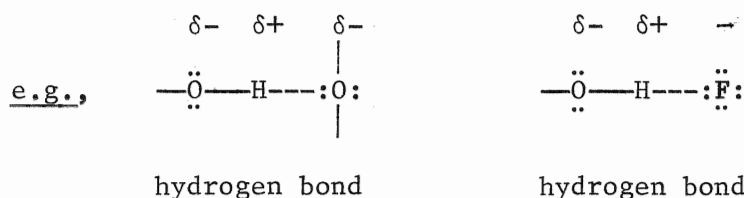
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## CHAPTER 1

## Introduction

## 1.1 Definition and classification of hydrogen bonding:

Hydrogen bonding is defined as an attraction between a hydrogen covalently bonded to a hetero-atom and another molecule (with its unshared electrons) or anion.<sup>1</sup>



Thus protic compounds such as alcohols, carboxylic acids, amines, phenols, naphthols, thiophenols etc. can form hydrogen bonds with hydrogen bond electron donors.

There is considerable spectroscopic and non-spectroscopic evidence to suggest that the fluoride ion is capable of forming strong hydrogen bonds to a variety of protic compounds.<sup>2,3,4</sup> Clark and Miller<sup>5</sup> reported hydrogen bonding of cyclic organic compounds, e.g., benzoic acid, phenol, 1,2-dihydroxybenzene, N-methylaniline, aniline, piperidine, pyrrolidine, phthalimide and benzene thiol with fluoride anion. Large shifts in the fundamental stretching vibration of the electron acceptor group have been reported, and values for the hydrogen bond enthalpy of fluoride-benzoic acid, fluoride-phenol and fluoride-1,2-dihydroxybenzene ( $113 \pm 5$ ,  $60 \pm 5$

and  $63 \pm 7 \text{ kJ mol}^{-1}$  respectively) have been predicted on the basis of correlations between the hydrogen-bond enthalpy and IR shift on hydrogen-bonding. In a review, Emsley<sup>6</sup> has classified hydrogen bonding into three classes, on the basis of IR spectroscopy (stretching mode of O-H bond):<sup>6</sup>

- (i) weak hydrogen bonds having their IR peaks not far from the non hydrogen bonding mode.
- (ii) strong hydrogen bonds having broad bands absorbing in the range  $3000\text{--}1600 \text{ cm}^{-1}$ .
- (iii) very strong hydrogen bonds giving a very broad band below  $1600 \text{ cm}^{-1}$ .

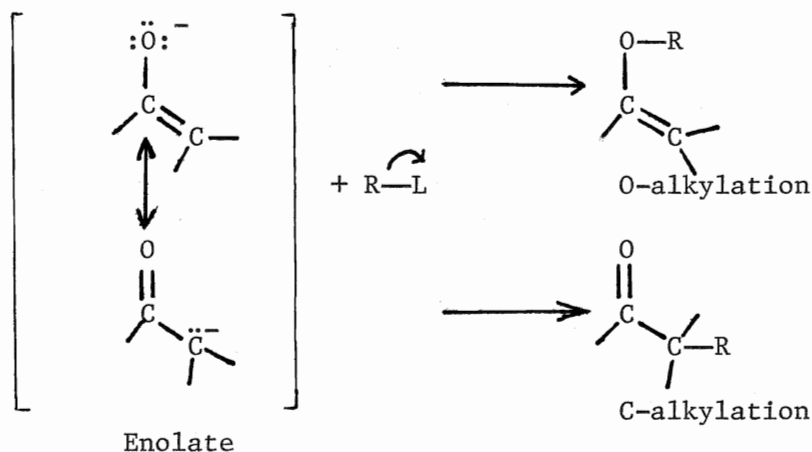
A few systems give spectra intermediate between (ii) and (iii), such as chloroacetic acid with strong oxygen bases like pyridine N-oxide, alkyl sulphoxides and phosphine oxides.<sup>7</sup> The formation of a hydrogen bond between an anion and an organic compound will result in the transfer of electron density from the anion to the organic moiety, thus enhancing the nucleophilicity of the organic species while at the same time reducing the nucleophilicity of the anion. This premise has been used to explain a variety of fluoride-promoted reactions.<sup>5,8-14</sup> Recently, ab initio LCAO-MO-SCF calculations have been performed by Emsley et al.,<sup>15</sup> on amide-fluoride complexes to determine their equilibrium structures and strength of the amide-fluoride hydrogen bond. At ca.  $148 \text{ kJ mol}^{-1}$ , it is the second strongest hydrogen bond known. They supported the findings by IR,  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectroscopic studies.

## 1.2 Alkylation of ambident anions:

Certain nucleophiles contain more than one atom bearing active electron pairs and so can react at either site and produce more than one product.<sup>16</sup> Such molecules or ions are called ambident nucleophiles. They are of two kinds:

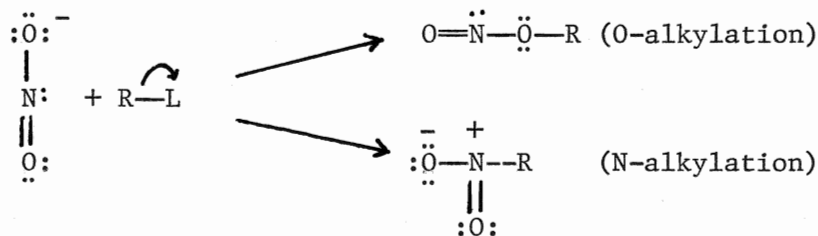
- (i) those in which resonance affords electron density from the active electron pair at either of the two (or more) sites

( $\ddot{X}-Y=Z \longleftrightarrow X=Y-\ddot{Z}$ ). Enolate anion is a fundamental example,



- (ii) Those with two different nucleophilic sites of similar reactivity.

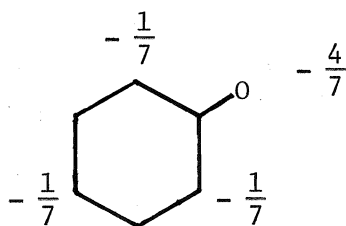
Nitrite anion is an example of this type.



When attention is focussed on the nucleophile only in an alkyl substitution reaction, it is called an alkylation reaction, implying attachment of an alkyl group  $R$  (from  $R-L$ ) to the nucleophile of interest. The atom of

attachment on the nucleophile is specified (C-, O-, N-, S-alkylation) and is important in clarifying ambident alkylations.

The most important feature, controlling the alkylation site with ambident nucleophiles is the relative electronegativity of the possible sites. The more electronegative the site  $O > N > C$ , where the major electron density is available, is alkylated with the  $S_N1$  character of the reactions and the less electronegative site is alkylated with the  $S_N2$  character. In the case of phenolate anion, most of the charge will reside on oxygen, and in many reactions with electrophiles, this is exclusively the site of attack. There is still a possibility of the reaction at carbons, though these atoms carry a minor part of charge density. In this respect, the theoretical calculation of  $\pi$  electron density is as shown in the diagram:<sup>17</sup>



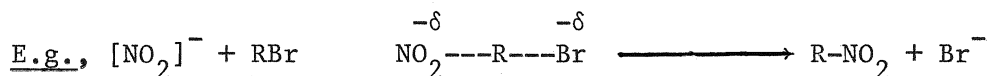
(charge distribution of phenolate anion calculated by molecular orbital theory neglecting electronegativity of oxygen atom)

In the studies of alkylation of sodium phenoxide and other phenol salts, Claisen and co-workers concluded that carbon alkylation occurs only at ortho position.<sup>18</sup>

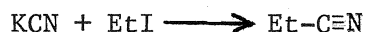
When an ambident anion is alkylated, a mixture of products is obtained. This problem was first noticed by Meyer and Stuber,<sup>19</sup> in 1872. By refluxing a mixture of amyl iodide and silver nitrite, they obtained the



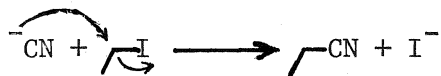
corresponding nitrite ester and nitroparaffin. The general reaction was  $RX + AgNO_2 \longrightarrow R-NO_2 + R-ONO$ . This reaction has been employed by numerous investigators for the preparation of aliphatic nitro compounds<sup>20</sup> but until 1954, it was not clear how pure nitro-paraffins could be prepared. Kornblum and co-workers<sup>21</sup> first suggested a simple procedure to get pure nitroparaffins by the action of alkyl halide and silver nitrite.<sup>21</sup> Through a series of works, Kornblum et al.<sup>22</sup> generalised about the alkylation of ambident anions, which was applicable even in the absence of silver, to solve the problem of C- versus O-alkylation; O- versus N-alkylation etc. in anions derived from acetoacetic ester, phenols, nitroparaffins,  $\alpha$ -pyridone, acid amides, thioamides etc. The greater the  $S_N1$  character of the transition state, the greater is the preference for covalent bond formation with the atom of higher electronegativity and the greater the  $S_N2$  contribution to the transition state the greater the preference for bond formation to the less electronegative atoms. They also reported that the reaction of silver nitrite with alkyl halides proceeds via a transition state which has both  $S_N1$  and  $S_N2$  character in proportions that vary gradually with the structure of halides. The tendency for alkyl nitrite formation i.e., O-alkylation can be promoted by using  $AgNO_2$ , because  $Ag^+$  promotes carbonium ion formation by precipitating the halide as  $AgX$ , e.g.,  $R-Br + Ag^+(NO_2)^- \longrightarrow AgBr + R^+ + NO_2^- \longrightarrow RONO$ . In the absence of  $Ag^+$  the resulting reaction was found to proceed by  $S_N2$  mechanism with preferential attack on the more polarizable atom of the nucleophile, resulting in the formation of nitro-alkane.



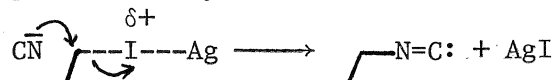
Kornblum and his associates reported that treatment of nitroparaffin salts with alkyl halides gave O-alkylation by an  $\text{S}_{\text{N}}2$  mechanism, a one-step process which is kinetically controlled. However, in Michael additions, they give C-alkylation, which is a multistage process and thermodynamically controlled. They proposed the electron transfer chain reaction for the latter.<sup>23</sup> The principle of hard and soft acids and bases also explains the idea of ambident reactivity.<sup>24</sup> For example, a cyanide ion can react with alkyl halide to give either nitrile or an isonitrile:



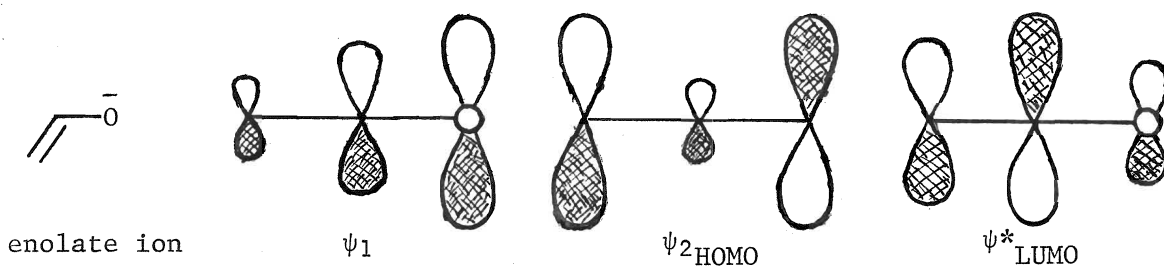
The hard and soft acid base principle tells us that a carbon atom is softer than a nitrogen atom of the nucleophile. So, for simple  $\text{S}_{\text{N}}2$  reactions, alkyl halides act as soft electrophiles and as a result the soft atom is alkylated.



When  $\text{Ag}^+$  is present, the halide ion is assisted in leaving the carbon, producing carbonium ion which is a hard electrophile, therefore the hard nucleophile is alkylated.



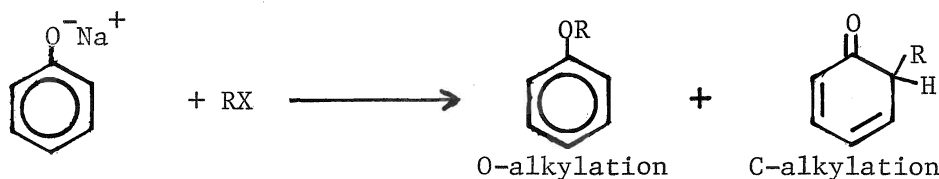
The reaction of enolate ion at carbon and oxygen has also been explained on Coulombic and frontier orbital terms.



The lowest energy orbital,  $\psi_1$ , is strongly polarized towards oxygen which has a large  $c$  (the co-efficients of the atomic orbitals) value. In the HOMO the  $c$ -values are the other way around, though not so strongly. Thus with charged electrophiles, the site of attack will be oxygen, kinetically with protons and carbonium ions. With electrophiles having little charge and relatively low lying LUMOS the reaction will take place at carbon.

### 1.3 Factors affecting the position of alkylation:

Work has been done by Curtin and his co-workers<sup>25,26</sup> and C. F. Hobbs et al.<sup>27</sup> to determine the factors which control the position of alkylation of an ambident anion. In 1926, Ingold<sup>28</sup> suggested that Claisen's ortho C-alkylation reaction of phenol salts with allyl and benzyl halides in non-polar solvents involve the reaction of alkyl halide with associated sodium phenoxide, whereas the oxygen alkylation in polar solvents was attributed to the reaction of dissociated phenoxide ion:<sup>28</sup>



Curtin et al.<sup>25</sup> reported that in the reaction of alkali metal salts of phenols, C-alkylation was increased at the expense of O-alkylation by using the following:

- (i) nonpolar solvents
- (ii) salts of less acidic phenols
- (iii) higher salt concentration
- (iv) salts of less electropositive alkali metals
- (v) more reactive halides (allylic rather than saturated halides)

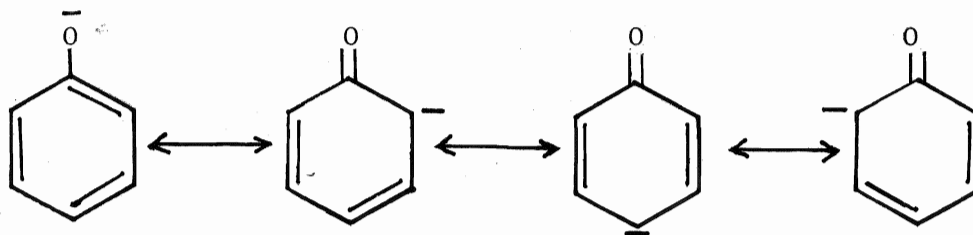
These factors were explained on the basis of suggestions of Ingold, Kornblum<sup>29</sup> pointed out that the position of alkylation of phenolic salts may depend to a large extent upon homogeneity and heterogeneity of the reaction mixture, i.e., C-alkylation is favoured by heterogeneous conditions and O-alkylation is favoured by homogeneous conditions. Some of these factors are discussed briefly as follows.

(i) Solvent effects: Much work has been done demonstrating that the medium in which the reaction is conducted may influence the mode of alkylation of an ambident anion. Hobbs et al.<sup>27</sup> reported in an alkylation of metal salts of pyrrole that the most polar solvent gives the highest percentage of 1-alkylation, i.e., the more electronegative atom is alkylated both under heterogeneous and homogeneous conditions.<sup>27</sup> It has also been reported that a good ionizing solvent (aprotic) leads to O-alkylation.<sup>30</sup> The activity of the carbanion is increased by co-ordination of the solvent with the cation.<sup>30</sup> In protic solvents, the more electronegative atom of the anion is solvated by hydrogen bonding with the solvent. As a result, the nucleophilicity of the electronegative atom is decreased, and a considerable amount of the less electronegative atom alkylated

product results<sup>31</sup> (Table 1). In polar aprotic solvents, the cation is solvated, more effectively than the anion. So the more electronegative atom of the nucleophile is freer from both solvent and cation. Therefore the change from nonpolar aprotic to polar aprotic solvent often increases the O-alkylation.

Another report was published by Kornblum et al. in 1963.<sup>32</sup> Reactions of sodium- $\beta$ -naphthoxide with benzyl bromide gave 95% O-alkylation in dimethyl sulfoxide and 85% C-alkylation in 2,2,2-trifluoroethanol. Finally they mentioned two properties of the solvent to account for the ability to control the course of ambident anion alkylation.<sup>32,33</sup>

(i) Their capacity for solvating ions, and (ii) their dielectric constants. Solvation depends in part upon hydrogen bonding between the solvents and the unshared electrons of the anions of the salt. The phenoxide ion is capable of bond formation at oxygen and at ortho and para ring carbons.



They found that in certain solvents, solutions of phenolic salts react to give much C-alkylation which is in contrast to the heterogeneous process,<sup>29</sup> and also C-alkylation takes place in both ortho and para position, which is again in contrast to the fact that only ortho alkylation was suggested by Kremer and his co-workers.<sup>18</sup> The reaction of sodium- $\beta$ -naphthoxide in THF gave 36% C-alkylation. This is due to the dielectric effect; a measure of which is the dielectric constant. Aprotic solvents of lower dielectric

Table 1. Nature of reaction of allyl and benzyl halide with solution of sodium phenoxide at 27°C.

Solvent	Percent of O-alkylation	Percent of C-alkylation
DMF	100	0
dioxane	100	0
ethanol	100	0
ethyleneglycol dimethyl ether	100	0
methanol	100	0
1-propanol	100	0
THF	100	0
water	55	45
phenol	25	75
2,2',3,3'-tetrafluoropropanol-1	45	55
2,2,2-trifluoroethanol	50	50

constant favour C-alkylation. Thus in protic solvents, hydrogen bonding capacity of the solvent controls the position of alkylation and in the aprotic solvents dielectric constant controls the position of alkylation, more polar solvents favouring O-alkylation, less polar solvents favouring C-alkylation.

(ii) Cation effects: In search of the factors controlling the position of alkylation, importance has also been given to the cations, as was first pointed out by Curtin and his associates.<sup>25</sup> Hobbs et al.<sup>27</sup> reported that for a given medium, both homogeneous and heterogeneous conditions, the relative percentage of more electronegative atom alkylated product increases with decreasing co-ordinating ability of the cation in the order  $\text{Li}^+ < \text{Na}^+ < \text{K}^+ < (\text{CH}_3)_3\text{-N}^+\text{Ph}$ . Kornblum<sup>32</sup> reported that in aprotic solvents of low dielectric constant, e.g., THF, the anion is likely to be a part of an ion aggregate, when it reacts. With small cation the ion pairs will be relatively tight. As we pass through  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{R}_4\text{N}^+$ , the ion pairs become progressively looser and the electrostatic constraint to ether formation gradually falls off. Thus the larger cation favours the more electronegative atoms to be alkylated, i.e., favours O-alkylation.

(iii) Steric effects: The structure of the ambident anion also controls the position of alkylation.<sup>34</sup> In the phenoxide ion, if the two ortho positions are substituted by large groups, then the ion becomes sterically hindered.<sup>35</sup> Unsubstituted phenoxide ion gives O-alkylation with methyl, ethyl and isopropyl iodide,<sup>29,32</sup> but 2,6-ditertiary butyl phenoxide ion

gave 88% O-alkylation and 6.9% C-alkylation with methyl iodide, 11% O-alkylation and 59% C-alkylation with ethyl iodide, and 100% C-alkylation with isopropyl iodide.<sup>34</sup>

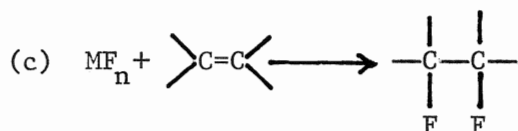
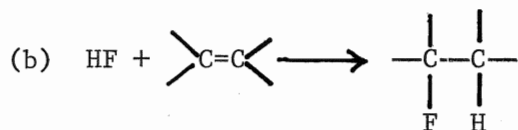
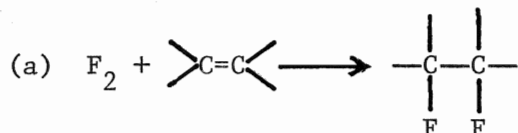
(iv) Effects of alkylating agents: The effect of alkylating agents was reported by Kurts and his co-workers.<sup>36</sup> The ratio of O versus C alkylation depends on (i) polar effect of the substituent in the alkylating agent, (ii) steric effect of the alkyl groups, and (iii) the symbiotic effect of the leaving group. The contributions from the first two depend on the nature of the leaving group. For halides R-X, an increase in the electron withdrawing ability of the X makes the carbon atom more partially positively charged, where the more electronegative atom of the anion can attack. Thus the ratio of O/C alkylation is increased in the order ROTs > RCl > RBr > RI. This has been explained as the positive inductive effect of the alkyl substituent at the reaction site of the alkylating agent depending on the nature of the leaving group and decreases in the order OTs<sup>-</sup> > Cl<sup>-</sup> > Br<sup>-</sup> > I<sup>-</sup>.

#### 1.4 Action of the fluoride ion:

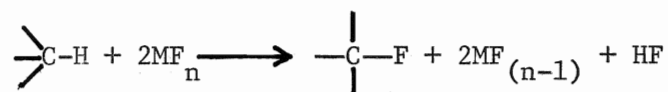
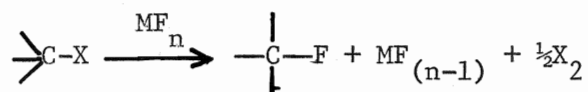
Alkali metal fluorides and quaternary ammonium fluorides are useful reagents in organic synthesis. They have been used in the past for more than two decades, as fluorinating agents and bases. Many organic fluorine compounds are useful in organic synthesis. For example, CF<sub>2</sub>=CF<sub>2</sub>, CF<sub>2</sub>=CFC1 and CF<sub>2</sub>=CH<sub>2</sub> react readily with alcohols, amines, mercaptans and with themselves to give other compounds containing functional groups such as ethers, amides etc.<sup>37</sup>



(i) As a fluorinating agent: To introduce fluorine into organic compounds, elemental fluorine, halogenated fluorine, hydrogen fluoride, metallic fluorides and organic fluorine compounds are used.<sup>38</sup> For example:

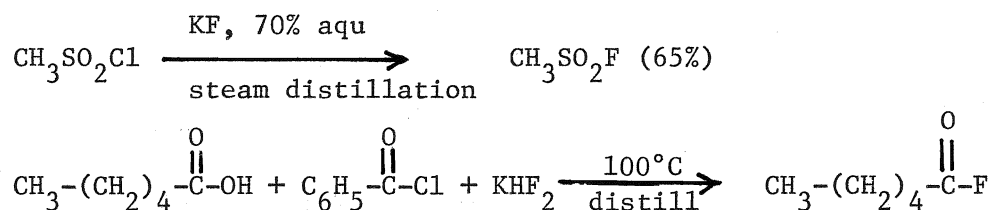


Among the metallic fluorides, high valency metallic fluorides have the capability of oxidative fluorination of alkanes, alkenes and ability of substituting fluorine for other halogens., e.g.,

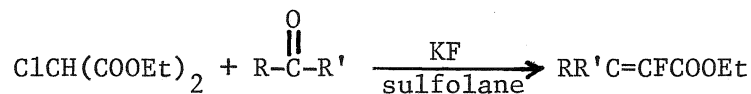


Group I and II fluorides, of which potassium fluoride is the most important, are used effectively to replace one or two halogens or an oxygenated group, such as an ester, with fluorine. Caesium and rubidium fluoride are more active than potassium fluoride, but they are very expensive and very hygroscopic. Sodium and lithium fluorides are almost ineffective in fluorinations.

Potassium fluoride substitutes fluorine for halogen in carboxylic acid halides, aromatic and alkyl sulphonyl halides,  $\alpha$ -haloesters, amides and nitriles, primary alkyl halides,  $\omega$ -halo alcohols, esters etc., e.g.,

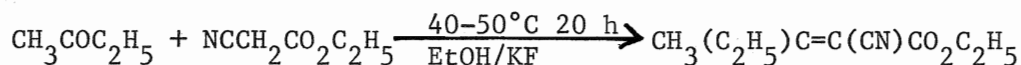
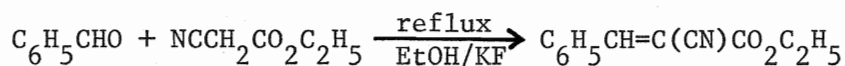


Now extensive work on potassium fluoride is being carried out by a group of Japanese chemists. Reactivity of the fluoride in KF depends on the means of drying, e.g., calcined, freeze-dried and spray-dried KF are now well known. Ishikawa and his co-workers<sup>39</sup> reported that organic compounds having activated halogen atoms can be readily fluorinated in acetonitrile with spray dried potassium fluoride. Freeze dried potassium fluoride was found to be much more effective as a hydrogen-bond forming catalytic reagent for alkylation of protic compounds than usual calcine-dried potassium fluoride.<sup>40</sup> 18-Crown-6 is an effective agent for the solubilization of KF in polar and non-polar aprotic solvents, to produce the so called naked fluoride ion. These naked fluoride ions are good fluorinating agents.<sup>41,42</sup> Kitazume and Ishikawa<sup>43</sup> reported one pot synthesis of  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters from chloromalonate ester and carbonyl compounds using spray dried KF.



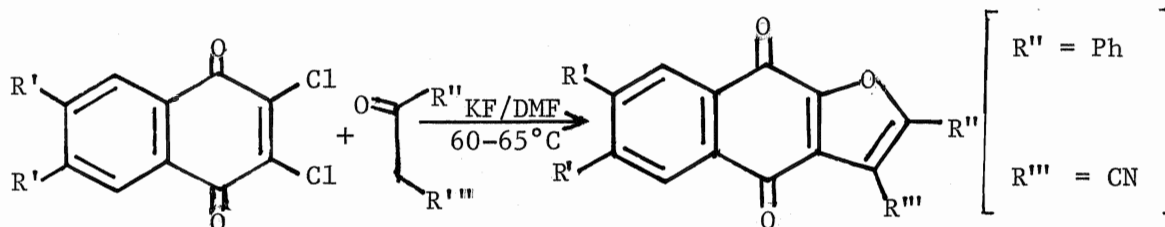
They also reported polyethylene glycol as an effective phase transfer catalyst in the fluorination of activated halogen compounds with KF in MeCN.<sup>44</sup>

(ii) As a base: The potential ability of the fluoride anion to act as a base might be predicted on considering the strength of the H-F bond ( $\sim 569 \text{ kJ mol}^{-1}$ ), cf. H-Cl  $\sim 432 \text{ kJ mol}^{-1}$ , O-H  $\sim 428 \text{ kJ mol}^{-1}$ , N-H  $\sim 314 \text{ kJ mol}^{-1}$ . On this basis, nucleophilic attack by fluoride towards other nuclei including silicon ( $E(\text{Si-F}) = 540 \pm 13 \text{ kJ mol}^{-1}$ ), phosphorus ( $E(\text{P-F}) = 439 \pm 96 \text{ kJ mol}^{-1}$ ) and carbon ( $E(\text{C-F}) = 536 \pm 21 \text{ kJ mol}^{-1}$ ) might be expected to be of possible synthetic value.<sup>45</sup> The basic character of fluoride ion was first reported by Nesmeyanov et al. in 1948.<sup>46</sup> In the reaction of trichloroacetic acid and potassium fluoride, they got chloroform instead of the expected trifluoroacetic acid. In organic chemistry there are many reactions which take place in the presence of base. Aldol condensation, Perkin condensation, Michael addition, Knoevenagel condensation etc. are examples of those reactions. After Nesmeyanov, Baba et al.<sup>47</sup> first tried fluoride ion as a base in 1958. They condensed active methylene compounds such as ethyl cyanoacetate, and diethyl malonate with aldehydes in the presence of potassium fluoride. They extended their work up to ketones.<sup>48</sup>

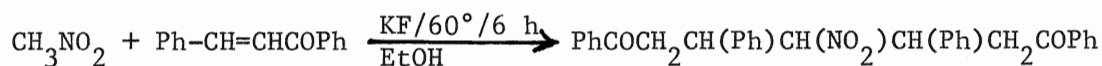


One of the first examples of a fluoride promoted O-alkylation was reported in 1957 by Kitano et al.<sup>49</sup> Fukui et al. reported C-alkylation of active methylene compounds, and N-alkylation of aniline and nuclear substituted anilines by alkyl halides, using potassium fluoride as condensing agent.<sup>50</sup> Kuo and co-workers<sup>51</sup> reported one step synthesis of

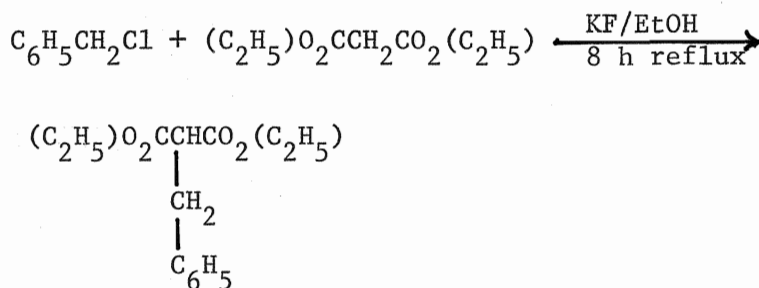
naphtho[2,3-b]-furan-4,9-diones directly from 2,3-dichloro-1,4-naphthoquinone and an active methylene compound in DMF in the presence of excess potassium fluoride.



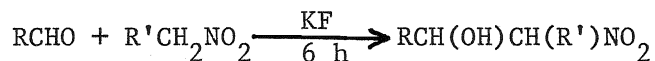
Ostaszynski and his associates<sup>52</sup> used potassium fluoride as catalyst for Michael addition of nitromethane to chalcone.



Patterson and Barnes<sup>53</sup> extended the potassium fluoride-catalyzed method to the reactions of a series of nitroalkanes with acrylamide and acrylonitrile using ethanol as solvent in excess. Sen and Sarma<sup>54</sup> found that in the presence of potassium fluoride, the alkylations are quite effective. A mixture of diethyl malonate and benzyl chloride in the presence of potassium fluoride in ethanol gave 68% diethylbenzyl malonate.

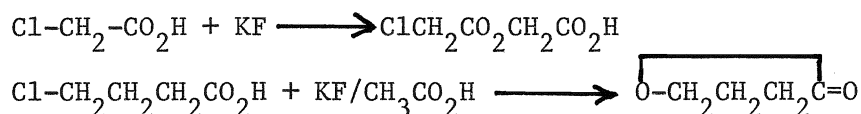


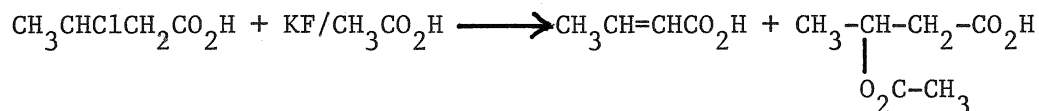
The use of potassium fluoride in aldol condensation between aldehydes and nitroalkanes has been described by several chemists.<sup>55,56,57</sup>



Other condensation reactions, elimination reactions of different type, intramolecular cyclization, heterocyclic ring formation, oxidation reactions etc. using potassium fluoride have been reported in the literature.<sup>45</sup>

(iii) As a hydrogen bond electron donor: The hydrogen bond forming ability of fluoride ion with the carboxylic acid was first discovered by Emsley.<sup>58</sup> The unexpected solubility of some alkali metal fluorides in acetic acid led him to conclude the hydrogen bonding between fluoride ion and acid hydroxyl hydrogen. This was supported by spectroscopic studies such as IR and  $^1\text{H}$  NMR, as well as thermodynamic studies.<sup>59</sup> Other halides such as chloride and bromide have also been reported to form hydrogen bonds with acetic acid.<sup>50</sup> In the IR spectra of potassium fluoride-acetic acid monosolvate and cesium fluoride-acetic acid monosolvate, the OH stretching frequency was shifted about  $2200\text{ cm}^{-1}$  from that of the acetic acid monomer at  $3600\text{ cm}^{-1}$ ; and in the  $^1\text{H}$  NMR, the chemical shift of the hydroxyl proton,  $\delta(\text{OH})$ , of these monosolvates, was found at 17.39 ppm. Thermodynamically, the bond enthalpy was calculated as  $120\text{ kJ mol}^{-1}$ .<sup>61,62</sup> When Clark and Emsley<sup>63</sup> tried to prepare fluoroacetic acid from chloroacetic acid using potassium fluoride, they got polymerization, lactonization and elimination reactions.





In these reactions, they did not consider fluoride ion as a base, they considered fluoride ion as a hydrogen bond electron donor. The fluoride ion transfers the electrons to the organic part of the complex, as a result the nucleophilicity of the organic part is increased and the course of reaction changes. This discovery provided a way to enhance the reactivity of some organic molecules capable of acting as hydrogen bond electron acceptor.

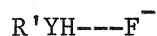
Clark and Miller<sup>13</sup> found a number of aromatic compounds, e.g., phenols, aniline and benzene thiol, can form strong hydrogen bonds with fluoride ion and react rapidly with alkyl halides, producing condensation products.

The general reaction was



where  $\text{R}'\text{Y} = \text{PhCO}_2^-$ ,  $\text{PhO}^-$ ,  $\text{PhS}^-$  and  $\text{PhN}^-(\text{Me})$

The hydrogen bond was explained as



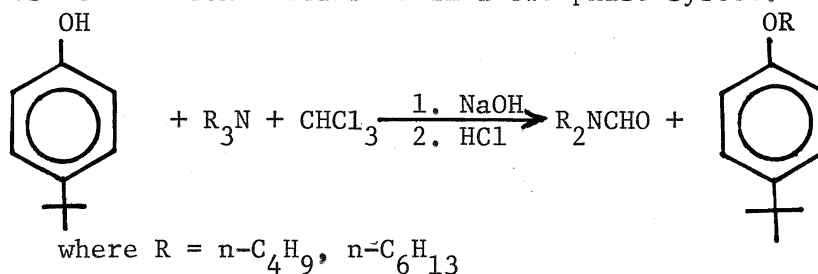
They also reported that  $\beta$ -diketones may be totally enolised in the  $\beta$ -diketone-tetraethylammonium fluoride monosolvate.<sup>64</sup> Treatment of this monosolvate with alkyl halides gave a high yield of mono C-alkyl product. They extended the work to prepare  $\alpha$ -thio- $\beta$ -dicarbonyl,<sup>65</sup> and to methylenation of catechols.<sup>13</sup> It is believed that the condensation or addition reactions are hydrogen bond assisted. The hydrogen bond between fluoride ion and methanol has been reported by Schleyer and Allerhand.<sup>66</sup> Bacelon et al.<sup>67</sup> found hydrogen bonding between fluoride ion and phenol.

### 1.5 Other hydrogen bond electron donors:

Like fluoride anion, there are several other bases which have the ability to form hydrogen bonds with phenols. Gurka and Taft<sup>68</sup> studied hydrogen bonding with p-fluorophenol by <sup>19</sup>F NMR and calorimetric methods. The bases like triphenylphosphine oxide, dimethyl sulphoxide, diphenyl ether etc. can form hydrogen bonds with protic compounds.<sup>68</sup> Taft et al.<sup>69</sup> established a free energy relationship in the formation of hydrogen bonded complexes of various hydroxyl reference acids with a wide variety of proton acceptors.

### 1.6 Other recent methods of alkylation of phenols:

Minoda et al.<sup>70</sup> reported O-alkylation of substituted phenols in the presence of dichlorocarbene in a two phase system.



The tertiary amine was used as alkylating agent and phase transfer catalyst as well. Tributyl phosphonium methylated polystyrene resin (phosphonium resin catalyst) has been used under triphasic reaction conditions for O-alkylation of phenols.<sup>71</sup> Phenols in raw coal naphtha were etherified by treatment with butyl bromide or butyl iodide in the presence of BaO or Ca(OH)<sub>2</sub> and DMF.<sup>72</sup>

Pasquini et al.<sup>73</sup> reported alkylation of phenoxide ion generated by potassium hydride in THF in the presence of a catalytic amount of [2:2:2]-cryptand. Alkylations of phenols, alcohols, amides and acids have been reported by using potassium hydroxide in DMF.<sup>74</sup> Recently phenols have been etherified by using ethyl fluorosulfonate (36-69% yields have been claimed).<sup>75</sup> Alekperov and Gasanov<sup>76</sup> reported the O-alkylation of substituted phenols by using aqueous sodium hydroxide. Diaryl ethers were prepared by the reaction of a halobenzene and alkali metal phenoxide in the presence of a corresponding phenol and a copper compound.<sup>77</sup> The synthesis of trifluoroethyl phenyl ether has been reported by reacting phenol with sodium hydroxide and  $\text{MeSO}_3\text{CH}_2\text{CF}_3$  at  $140^\circ\text{C}$ .<sup>78</sup> Koki and Taketoshi<sup>79</sup> prepared mono-, di- and trialkyl phenols by heating alkali metal salts of phenols with aliphatic alcohols and phenols with alkali metal carbonates and aliphatic alcohols.<sup>79</sup> Treatment of aminophenols with alkyl or benzyl halide in MeCN in the presence of benzyl trialkyl ammonium salts and alkali metal hydroxides produced aminophenyl alkyl or aminophenyl benzyl ether.<sup>80</sup>



## Chapter 2

### Aim of This Work

From the literature survey, it is observed that fluoride ion assisted alkylation of phenols is the most efficient of the methods, considering the reaction conditions, yield, ease of workup and commercial availability of the chemicals, as well as the recovery of catalyst. The fluoride ion assisted alkylations are thought to be hydrogen bond assisted reactions. A recent study has emphasized how important hydrogen bonding is, in determining the course and rate of alkylation reactions of naphthols and phenols.<sup>81</sup> As a part of these studies, the present work considers the influence of solvent in the fluoride assisted reactions, particularly with regard to the localization of the hydrogen bond charge density. To account for the importance of hydrogen bonding, various solvents, e.g., toluene, benzene, hexane and DMF, various catalytic agents, e.g., potassium t-butoxide, various fluorides and triphenylphosphine oxide; and various phenols have been used in this research. The presence of water in these reactions is a very important factor to be considered, one which can decrease the yield drastically. A measure of the tolerance to water in the alkylation reaction of phenol has been carried out. In addition, the action of fluoride ion with phase transfer catalysts has also been studied.

## Chapter 3

### Experimental Work

#### 3.1 Instrumentation:

Proton nuclear magnetic resonance spectra ( $^1\text{H}$  NMR) were recorded on a Varian A-60 CW spectrometer operating at 60 MHz, a Bruker WP-60 FT spectrometer operating at 60 MHz and a Bruker WP-80 CW spectrometer operating at 80 MHz with tetramethylsilane as an internal reference.

Infrared spectra were recorded on a Perkin-Elmer Model 237B grating infrared spectrophotometer using standard liquid film and potassium bromide pellet techniques.

Mass spectra were recorded on an AEI MS-30 double beam, double focussing mass spectrometer, interfaced to a Kratos DS55 data system. Gas liquid chromatography/mass spectrometry analyses were carried out with a 3% SE30 Chrom W (80-200 mesh) column in a Pye 104 GC interfaced to the MS 30 double beam mass spectrometer via a Bieman-Watson interface.

Melting points were determined on a Kofler hot stage microscope apparatus and are uncorrected.

#### 3.2 Chemicals used:

For this work, phenols of interest were phenol, p-nitrophenol and 2,6-di-tert-butyl-4-methylphenol. The alkylating agents were benzyl bromide and benzyl chloride. Solvents of interest were non polar aprotic e.g., toluene, benzene, hexane, then polar aprotic, e.g., N,N'-dimethyl

formamide and dimethyl sulfoxide. The catalysts were potassium t-butoxide, fluoride anion and triphenyl phosphine oxide. Their sources and purification are described below.

Analytical reagent grade phenol (BDH) was used after drying in a vacuum line for about 36 hours. Laboratory reagent grade p-nitrophenol (BDH) was re-crystallized in water and dried in a vacuum line for about 36 hours. Laboratory grade 2,6-di-tert-butyl-4-methylphenol (Aldrich) was used without further purification and drying. General purpose reagent grade benzyl bromide (BDH) and reagent grade benzyl chloride (Fisher Scientific Company) were used without further purification.

Laboratory reagent grade (BDH) toluene and laboratory reagent grade benzene were used after distillation and drying over molecular sieves of type 5A (BDH). Laboratory reagent grade hexane (BDH) was used without distillation, but dried over sodium wire. Laboratory reagent grade (BDH) DMF was used either with or without distillation, but dried over molecular sieves of type 5A. Potassium t-butoxide was a commercial sample, laboratory grade (Aldrich), used without further purification or drying. Potassium fluoride was a commercial (Aldrich, anhydrous KF) dried either in the oven at  $\sim 250^{\circ}\text{C}$  for several hours or by freeze drying. For freeze drying, a saturated aqueous solution of KF was kept in the refrigerator until solidified completely. The solid potassium fluoride hydrate was put into the vacuum line at room temperature for several days until dried completely.

Tetrabutylammonium fluoride was prepared in aqueous solution by neutralisation of tetrabutylammonium hydroxide (aqueous commercial sample,

Aldrich) with 48% hydrofluoric acid. The aqueous solution was evaporated in a rotary evaporator until some solids appeared. Then acetonitrile was added and evaporated again; the process of washing with acetonitrile was repeated several times and the sample was finally put on the vacuum line for several days until it solidified.

Triphenylphosphine oxide was a commercial sample (Aldrich) and was used without purification and/or drying. Tetrabutylammonium bromide was a commercial sample (Eastman-Kodak) used without purification and/or drying.

18-Crown-6 was a commercial sample (Aldrich) and dried as follows: about 5 mL of nitromethane was added to 3.5 g of 18-crown-6, the mixture was cooled to about  $-10^{\circ}\text{C}$ , then the nitromethane was evaporated by rotary evaporator. The process was repeated three times, and the 18-crown-6 was put on the vacuum line for 48 hours.

### 3.3 Typical reactions:

All the reactions were monitored by  $^1\text{H}$  NMR spectroscopy, specifically the chemical shift change of benzylic protons of the benzyl halide. The other techniques were almost the same for various phenols in various solvents. Details of the experimental procedure are given below.

(i) Reactions of phenols with benzyl bromide in the presence of strong base: In these reactions, potassium-*t*-butoxide was used as the base. The alkylations were done first in toluene and then in DMF. Potassium-*t*-butoxide was poorly soluble in toluene; the solubility was increased by using an excess of dry 18-crown-6.

Phenol (0.01 mole) was dissolved in 20 mL toluene, then potassium t-butoxide (0.63 g, 0.0057 mole) was added to the solution, followed by the addition of 18-crown-6 (1.18 g, 0.0068 mole). The mixture was well stirred by magnetic stirrer and made a homogeneous solution. To this solution, benzyl bromide (0.01 mole) was added, and the solution was stirred again. After 10 minutes, the  $^1\text{H}$  NMR spectrum showed about 46% conversion of the starting material (benzyl bromide). After 10 hours, the reaction mixture was heated for about 10 hours at  $\sim 70^\circ\text{C}$ , but no remarkable change in the amount of conversion was noticed. The reaction mixture was extracted with ether, washed three times with water, dried (magnesium sulphate) and the ether evaporated. A light brown coloured liquid was obtained.  $^1\text{H}$  NMR spectrum of this solution showed 48% benzyl bromide had been consumed. GC/mass spectra showed only one product. This was chromatographed on a column of neutral alumina using pentane as eluent. After evaporation of the eluent, the product was crystallised from 60% ethanol. The product was benzyl phenyl ether (0.52 g, 28%). The melting point was  $38-39^\circ\text{C}$ , consistent with the literature m.p. ( $39^\circ\text{C}$ ).<sup>82</sup> The identity of the product was established by  $^1\text{H}$  NMR, IR and mass spectrometry.

Benzyl phenyl ether:  $^1\text{H}$  NMR:  $\delta = 5.1$  (s, 2H), centered at 7.1 (m, 5H), 7.4 (s, 5H).

IR:  $1250\text{ cm}^{-1}$  (Ar-O-C asymmetric stretching),  
 $1220\text{ cm}^{-1}$  (Ar-O-C symmetric stretching).

Mass spectrum:  $m/z = 184$  ( $\text{M}^+$ ),  $m/z = 91$  (base peak).

In DMF, potassium t-butoxide was readily soluble and hence no crown ether was used. Potassium t-butoxide was used as a 1:1 mole ratio with phenol. The other techniques were the same as described earlier. Fifteen minutes after the addition of benzyl bromide, the  $^1\text{H}$  NMR spectrum showed no starting material. The reaction mixture was extracted with ether, dried and chromatographed. After crystallisation, 62% benzyl phenyl ether was obtained.

p-Nitrophenol was not soluble in toluene, but when potassium t-butoxide with 18-crown-6 was added to the mixture of nitrophenol in toluene, a homogeneous solution was produced. Thus, potassium t-butoxide (0.63 g, 0.0057 mole), 18-crown-6 (1.82 g, 0.0069 mole) and 0.01 mole of p-nitrophenol were dissolved in 20 mL toluene. To this homogeneous solution, 0.01 mole benzyl bromide was added and well stirred. After 15 minutes, the  $^1\text{H}$  NMR spectrum showed about 50% conversion of the benzylic peak. The reaction mixture was heated at about  $70^\circ\text{C}$  up to 12 hours, but no remarkable change was noticed. The reaction mixture was extracted with ether, washed with water, dried (magnesium sulphate) and evaporated. A solid product was obtained. GC/mass spectrometry showed only one product. The product was crystallised from 60% ethanol. Benzyl-4-nitrophenyl ether (0.75 g, 33%) was obtained. The product was analysed by  $^1\text{H}$  NMR, IR and mass spectrometry.  $^1\text{H}$  NMR:  $\delta = 5.2$  ppm (s, 2H), 7.45 (s, 5H), centered at 7.65 (AA', BB', 4H).

IR:  $1500\text{ cm}^{-1}$  ( $\text{NO}_2$  stretching),  
 $1250\text{ cm}^{-1}$  (Ar-O-C, asymmetric stretching)  
 $1005\text{ cm}^{-1}$  (Ar-O-C, symmetric stretching).

Mass spectrometry:  $m/z = 229 (M^+)$ . The m.p. was 105–106°C, consistent with the literature m.p. (106°C).<sup>83</sup>

In DMF, both p-nitrophenol and potassium t-butoxide were soluble, therefore potassium t-butoxide and nitrophenol were used in 1:1 mole ratio, and the rest of the techniques were the same as described earlier. In DMF, the isolated yield was 71% benzyl-4-nitrophenyl ether. Similar techniques were used to alkylate 2,6-di-tert-butyl-4-methylphenol in both toluene and DMF, but no alkylated product was obtained.

(ii) Reactions of phenols with benzyl bromide in the presence of fluoride anion: These reactions were divided into two classes: (A) heterogeneous reactions, (B) homogeneous reactions. In heterogeneous reactions, potassium fluoride was used as the source of fluoride ions, dried either by heating in the oven or by freeze-drying. In homogeneous reactions, tetrabutylammonium fluoride was used as the source of fluoride ions.

(A) Heterogeneous reactions: The techniques used in each case were the same, unless specified. Details of a representative preparation are described below: Reaction of phenol with benzyl bromide in DMF: Benzyl bromide (0.01 mole), phenol (0.01 mole) and potassium fluoride oven dried (0.02 mole) in 20 mL DMF were heated to about 60°C with constant stirring. The reaction was stopped after 24 hours, when the  $^1\text{H}$  NMR spectrum showed no starting material (benzyl bromide) remaining. The reaction mixture was extracted with diethyl ether, washed with water at least three times, then dried over magnesium sulphate. The ether was evaporated by rotary evaporator, when a brown coloured liquid (with some solids also) was

obtained. GC/mass spectrometry of this product showed benzyl fluoride and benzyl phenyl ether. The product was chromatographed using a column of neutral alumina and pentane as eluent. After crystallisation from 60% alcohol, benzyl phenyl ether (1.23 g, 67%) was obtained.

When toluene was used as solvent in the reaction of phenol and benzyl bromide, the conversion was small, therefore the products were analysed by GC/mass spectrometry only.

(B) Homogeneous reactions: The techniques used for all phenols in various solvents were the same; a representative description is given below:

Reaction of phenol with benzyl bromide in DMF in the presence of tetrabutylammonium fluoride: Phenol (0.01 mole) was mixed with tetrabutylammonium fluoride (0.02 mole) and the mixture was dried again by rotary evaporator at about 60°C for 20 minutes and finally in vacuum line for about 12 hours. To this mixture, 20 mL DMF was added, followed by addition of benzyl bromide (0.01 mole). The mixture was stirred at room temperature. After 75 hours, the  $^1\text{H}$  NMR spectrum showed no starting material. The reaction mixture was extracted with ether, washed with water, dried (magnesium sulphate) and evaporated. The product was analysed by GC/mass spectrometry. A mixture of products was obtained, cf. Table V.

(iii) Reactions of phenols in the presence of triphenylphosphine oxide: Alkylations were attempted only for phenol and p-nitrophenol. p-Nitrophenol (0.01 mole, triphenylphosphine oxide (0.04 mole) and benzyl bromide (0.01 mole) in 20 mL DMF was heated at about 70°C up to seven days, but the  $^1\text{H}$  NMR spectrum showed the starting material remaining unchanged.



The reaction mixture was extracted with ether, washed with water, dried (magnesium sulphate) and after the solvent was evaporated, analysed by GC/mass spectrometry, which showed the starting materials only. Similar techniques were used for the attempted alkylation of phenol.

#### 3.4 $^1\text{H}$ NMR studies of hydrogen bonding between phenol and triphenylphosphine oxide:

1 M solution of phenol in  $\text{CDCl}_3$  was prepared separately in nine vials. The chemical shift  $\delta(\text{OH})$  of the phenol of one of these solutions was measured at ambient temperature ( $36^\circ\text{C}$ ). To the rest of the solutions, triphenylphosphine oxide was added in various mole ratios: 1:0.125, 1:0.25, 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 (phenol:triphenylphosphine oxide). The chemical shifts  $\delta(\text{OH})$  of these solutions were measured at  $36^\circ\text{C}$ . The chemical shifts were plotted against the mole ratio of triphenylphosphine oxide. All the chemical shifts downfield of the reference compound were assigned as positive shifts.

The chemical shifts  $\delta(\text{OH})$  of phenol in carbon tetrachloride and hexane were measured at the same temperature. For this purpose, 0.05 M, 0.1 M, 0.25 M, 0.5 M and 1.0 M solutions in carbon tetrachloride and hexane were prepared separately and the chemical shifts of the OH proton of phenol of these solutions were measured. The chemical shifts downfield of the reference compound were assigned as positive shifts, and plotted against the molarity of the phenol.

### 3.5 Use of fluoride ion (potassium fluoride) with phase transfer catalysts:

Tetrabutylammonium bromide was used as the phase transfer catalyst and benzyl chloride was used as the alkylating agent. Phenol (0.01 mole), benzyl chloride (0.01 mole), potassium fluoride (0.02 mole) and tetrabutylammonium bromide (0.02 mole) in 20 mL DMF was heated at about 100°C. After 5½ hours, the  $^1\text{H}$  NMR spectrum showed no starting material remained. The reaction mixture was extracted with ether, washed with water, dried (magnesium sulphate), the solvent evaporated and the residue chromatographed. The product was benzyl phenyl ether (1.08 g, 59%). The amount of tetrabutylammonium bromide was decreased gradually down to 0.0002 mole, cf. Table VIII.

### 3.6 Study of the influence of water in the alkylation reactions of phenol:

Phenol (0.01 mole), benzyl bromide (0.01 mole), potassium fluoride (0.02 mole) and water (0.01 mole) in 20 mL DMF was heated at about 80°C. After two hours, the  $^1\text{H}$  NMR spectrum showed no starting material remained. The reaction mixture was extracted with ether, washed with water, dried (magnesium sulphate) and chromatographed. The isolated yield of ether was 0.6 g (33%). The amount of water was increased gradually up to 0.1 mole, when no appreciable amount of benzyl phenyl ether was obtained, cf. Table IX.

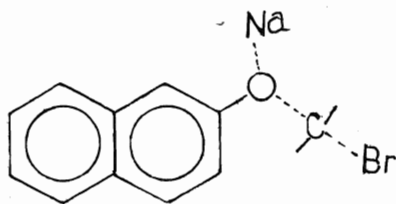
## Chapter 4

## RESULTS AND DISCUSSION

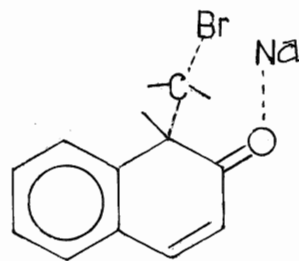
4.1 It has been mentioned that phenol has two sites for alkylation. C-alkylation is important in synthetic chemistry because it increases the carbon chain. The O-alkylation reaction is important in the synthesis of ethers. The common conventional method for the preparation of ethers is the Williamson synthesis. Several modifications of the Williamson synthesis have been developed,<sup>84</sup> including those employing diazomethane (for methylation),<sup>85,86</sup> phase transfer catalysis,<sup>87</sup> tetraalkylammonium phenoxides,<sup>88</sup> sodium hydride,<sup>89</sup> anion exchange resins<sup>90</sup> and fluoride anions.<sup>91</sup> Among all these methods, the fluoride ion method has been reported to be the best and most efficient, via what has been described as a hydrogen bond assisted reaction. There are several factors to be considered for the conventional methods of alkylation of phenols,<sup>25</sup> among them the solvent effect is one of the most important. In the present work, the influence of solvent in hydrogen bond assisted alkylation reactions of phenols is discussed. The localization of the hydrogen bond charge density, the influence of water in the reaction and the use of fluoride with a phase transfer catalyst have also been considered during these alkylation reactions.

#### 4.2 Alkylation reactions of phenols in the presence of strong base:

Toluene and DMF were used as solvents in these reactions. In toluene, the products were the ether for both phenol and p-nitrophenol alkylations. No C-alkylated product was obtained (cf. Table II). The conversion (benzyl bromide consumed) was about 48% and 50% for phenol and p-nitrophenol, respectively. It has already been reported<sup>32</sup> that sodium- $\beta$ -naphthoxide reacts with benzyl bromide in a nonpolar aprotic solvent such as tetrahydrofuran to produce a substantial amount of the C-alkylated product. To account for the effect of aprotic solvent of low dielectric constant, it was suggested that the sodium- $\beta$ -naphthoxide exists as contact ion pairs and as higher aggregates. The O-alkylation is disfavoured in the non-polar aprotic solvent by the large separation of the sodium cation and the developing halide ion in the transition state [A] as shown below. On the other hand the C-alkylation is favoured in the transition state [B].



[A]



[B]

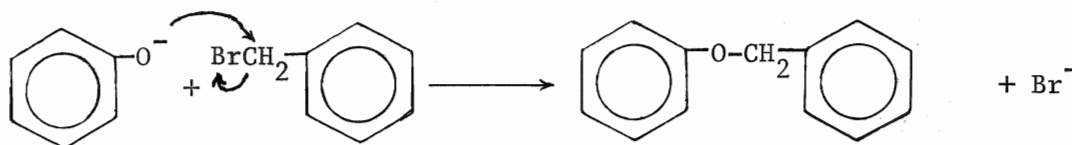
Table II. Reactions of various phenols with benzyl bromide in the presence of potassium t-butoxide, in toluene and DMF as solvents.

Phenols used	Catalyst	Solvent	Temperature	Time	Conversion*	Product	Isolated Yield
phenol	potassium t-butoxide + crown ether	toluene	70°C	14 h	48%	ether	28%
phenol	potassium t-butoxide	DMF	23°C	~10 min	100%	ether	61%
p-nitrophenol	potassium t-butoxide + crown ether	toluene	70°C	3 h	50%	ether	31%
p-nitrophenol	potassium t-butoxide	DMF	23°C	~10 min	100%	ether	71%
2,6-ditertiarybutyl-4-methyl phenol	potassium t-butoxide + crown ether	toluene	70°C	24 h	46%	mixture	
2,6-ditertiarybutyl-4-methyl phenol	potassium t-butoxide	DMF	70°C	12 h	100%	mixture	

\*The percent of conversion was based on the percentage of benzyl halide consumed.

O-alkylation involves the transfer of charge from oxygen to bromine, and since bromine is relatively remote from the sodium, this must be accomplished against the attractive force exerted by the sodium ion. The attractive force exerted by the sodium ion on the departing bromide ion is greatest in nonpolar aprotic solvents. In contrast to the linear oxygen-carbon-bromine disposition which characterizes O-alkylation, the C-alkylation proceeds through a non-linear arrangement which suggests that the developing bromide ion is relatively close to the sodium ion.

In the case of the alkylation of phenol and p-nitrophenol using potassium t-butoxide and a crown ether such as 18-crown-6 in toluene, the potassium cation forms a complex with the crown ether, and as a result the phenoxide ion and the potassium ion may not be present as contact ion pairs. They could exist as solvent separated ion pairs or dissociated ion pairs. Therefore the phenoxide anion and the p-nitrophenoxide anion may be less shielded by the cation and by the solvent. They act as nucleophiles when they react with benzyl bromide to produce an ether according to the following reaction:



A similar mechanism applies to the alkylation of p-nitrophenol. From these results, it may be suggested that the negative charge of the phenoxide ions was not delocalised into the ring. The low conversion to the product was due to the low solubility of potassium t-butoxide. The conversion yield might be increased by using a dilute solution and an excess of the potassium t-butoxide and the crown ether.

The alkylation of 2,6-di-tert-butyl-4-methylphenol did not give any O- or C-alkylated product, rather gave a mixture of various products. The mixture could not be well separated and remained unidentified.

In DMF, the reactions were carried out without crown ether, because the use of crown ether in DMF is not effective.<sup>45</sup> The amount of potassium t-butoxide was used as a 1:1 mole ratio with phenols. The products were O-alkylated compounds. The reaction conditions were found to be different from those in toluene (cf. Table II). At room temperature, the reactions were found to be completed within about 10 minutes. From these reactions, it appeared that in polar aprotic solvents such as DMF, phenoxide ion can be rather easily generated by a strong base such as potassium t-butoxide. In DMF, the cations and the phenoxide anions exist as solvated ions (separated). It was suggested<sup>32</sup> that in polar aprotic solvents such as DMF, the cation is relatively more solvated than the anions. Thus in DMF, the anion has not only got away from the cation, but has something approaching the character of a "free" anion including a high degree of reactivity. Therefore it may be observed that the rate of O-alkylation in phenols has increased significantly in the polar aprotic solvent as

compared to the nonpolar one. The above observations were found in quite good agreement with the results reported by Kornblum.<sup>32</sup> In the case of 2,6-di-tert-butyl-4-methylphenol, no alkylated product was produced even at higher temperature in DMF.

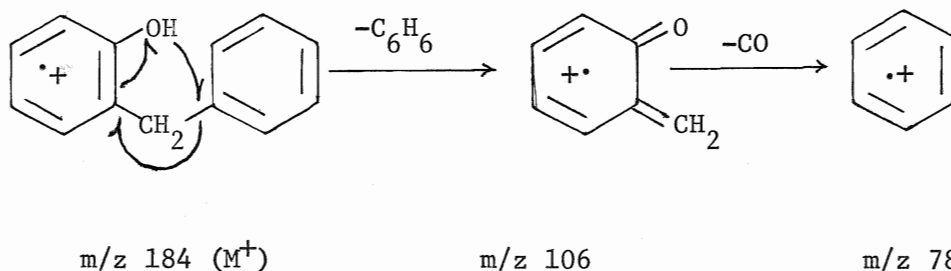
Attempts to alkylate phenol using catalytic amounts of the base (about 0.0004 mole) in DMF were made, but no significant amount of ether was produced. From this observation, it may be suggested that generation of the phenoxide ion was essential for the alkylation reaction in the presence of the base. In the Williamson synthesis,<sup>92</sup> the sodium salts of phenols produce sodium ion and phenoxide ion in solution. Thus in the alkylation reaction of phenols, the amount of the base used is very important. The base reacts with phenols producing phenoxide ion and the cation of the base in solution. Therefore in the base assisted reactions, it may be suggested that the rate of alkylation of phenols depends on the concentration of the phenoxide ion. This observation was found in good agreement with the result obtained by Kornblum.<sup>33</sup>

#### 4.3 Alkylation reactions of phenols in the presence of fluoride ion:

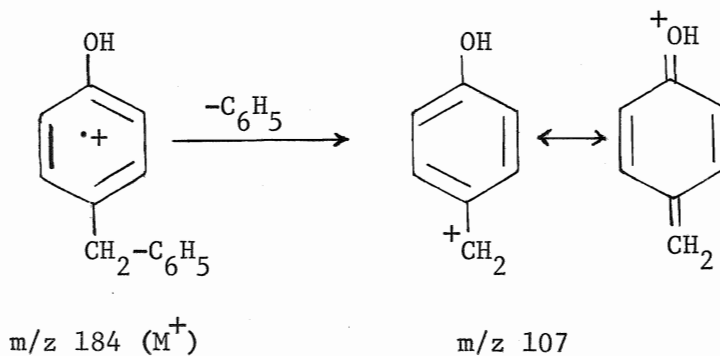
(A) Heterogeneous reactions; These reactions were tried in nonpolar aprotic solvents as well as in polar aprotic solvents. In toluene, phenol gave only C-alkylated products when potassium fluoride (oven dried) was used in the reaction. The conversion was low, about 20%. The product was analysed by GC/mass spectrometry. Two fractions from GC/mass spectrometry gave a molecular ion ( $M^+$ ) of  $m/z$  184, consistent with the alkylated product



of phenol, but their fragmentation patterns were found to be different (cf. mass spectra in the Appendix). One compound gave the fragmentation as  $m/z$  184, 106, 183, 91, 176, 78 in the decreasing order of intensity, which is consistent with the ortho-benzyl phenol. The molecular ion can rearrange by losing 78 mass units of benzene, giving the odd electron ion of  $m/z$  106, as shown in the mechanism below.



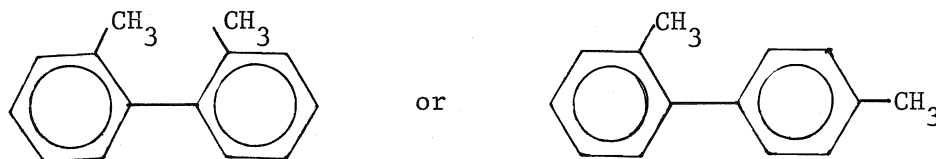
The peak at  $m/z$  106 was observed to be more prominent in this compound. The other compound had the fragmentation pattern,  $m/z$  184, 183, 107, 106, 165, 91, 77, consistent with *p*-benzyl phenol. For the *p*-benzyl phenol, the loss of 77 mass units by simple benzylic cleavage<sup>92</sup> was predominant, giving rise to the even electron ion of  $m/z$  107, as shown below.



These compounds were further confirmed as C-alkylated phenol by treatment with *t*-butyldimethylsilyl chloride. The silyl derivatives were analysed

by GC/mass spectrometry. Both the compounds gave the same molecular weight, ( $M^+$ ) of 298 m/z (silyl derivative of phenols). The loss of 57 mass units (t-butyl) and 28 mass units (silicon) was common in both the compounds. The peak at m/z 91 was 100% and m/z 241 ( $M^+ - 57$ ) was also very intense. The  $^1\text{H}$  NMR spectrum of the reaction mixture after extraction with ether showed the chemical shift of the benzylic protons at  $\delta = 3.9$  ppm (singlet) which was also consistent with the literature value<sup>93</sup> ( $\delta = 3.9$  ppm) of p-benzyl phenol cf. Figure A6 in the Appendix.

In this alkylation reaction of phenol in toluene, two other byproducts were observed. One compound was identified from the mass spectral data and literature search to be 2,2'-dimethylbiphenyl or 2,4'-dimethylbiphenyl.



2,2'-dimethylbiphenyl

2,4'-dimethylbiphenyl

The molecular ion of the compound was 182 ( $M^+$ ); the spectrum is shown in the Appendix. The origin of these compounds was not clear. Wibent et al.<sup>94</sup> reported that diphenyl compounds can be formed in small quantities from benzene, heated to about 400°C in the presence of iodine or hydrogen iodide. Therefore, as the reaction was done in toluene, it could be possible to form the 2,2'- or 2,3'-dimethylbiphenyl compound from toluene, though here the conditions observed were much different. The solvent, toluene, was analysed by GC/mass spectrometry, which showed no trace of

Table III. Reactions of various phenols with benzyl bromide in the presence of fluoride in various solvents. Heterogeneous reactions.

Phenols used	Catalyst	Solvent	Temperature	Time	Conversion*	Product Isolated	Yield
phenol	potassium fluoride	toluene	60°C	77 h	20%	C-alkylated product	
phenol	potassium fluoride	DMF	60°C	24 h	100%	ether	67%
p-nitrophenol	potassium fluoride	toluene	82°C	72 h	0	--	
p-nitrophenol	potassium fluoride	benzene + 5% DMF	60°C	32 h	100	ether	75%
p-nitrophenol	potassium fluoride	DMF	60°C	19 h	100	ether	76%
2,6-ditertiarybutyl-4-methyl phenol	potassium fluoride	toluene	82°C	72 h	0	--	
2,6-ditertiarybutyl-4-methyl phenol	potassium fluoride	DMF	82°C	24 h	0	--	

\*The percent of conversion was based on the percentage of benzyl halide consumed.

such compounds in the solvent. The other compound was observed on the gas chromatograph as a tail of p-benzyl phenol. The compound was not well separated from p-benzyl phenol; it was a very small fraction and remained unidentified. The potassium fluoride/toluene system was exceptional only where C-alkylated products were obtained. Potassium fluoride was much less soluble in toluene, essentially insoluble. So and Miller<sup>95</sup> have suggested that in the KF/DMF method in the hydrogen bond assisted reactions, the reaction might be occurring in part on the surface of the suspended fluoride. In comparison with the potassium fluoride/toluene system, it appeared that, in KF/DMF the reaction occurred at least in part, in solution, whereas in the potassium fluoride/toluene system, the reaction occurred entirely on the surface of the suspended fluoride. From these C-alkylated products, it may be suggested that the charge density was completely delocalised into the ring during the alkylation reaction of phenol.

In DMF, the main product was found to be the benzyl phenyl ether. When oven-dried potassium fluoride was used in the reaction, benzyl fluoride was obtained as a byproduct. The reaction time observed was significantly less as compared to when toluene was used as a solvent. In these hydrogen bond assisted reactions, it was also observed that the solvent played a very important role. The nonpolar aprotic solvents like toluene gave C-alkylation whereas the polar aprotic solvents, such as DMF, changed the course of the reaction and produced the O-alkylated products. The rate of alkylation was also changed and increased with the change of the solvent from nonpolar aprotic to polar aprotic.

p-Nitrophenol was found to be insoluble in toluene and benzene. When a reaction was tried in toluene, no alkylation took place, only starting materials were found after extraction. Therefore the reaction of p-nitrophenol was run in the mixed solvent, benzene with 5% DMF. The product was identified as the O-alkylated compound only, i.e., benzyl 4-nitrophenyl ether. In the reactions of p-nitrophenol, it was difficult to infer much about the solvent activity, as mixed solvents were used, but considering the reaction time, it may be suggested that the rate of alkylation increased with the increase of solvent polarity. No byproduct such as benzyl fluoride was formed in the alkylation of p-nitrophenol, though the same potassium fluoride (oven dried) and solvent DMF were used.

The alkylation of 2,6-di-tert-butyl-4-methylphenol was attempted in both toluene and DMF using potassium fluoride, but no alkylated product was obtained. After extraction of the reaction mixture, GC/mass spectrometry showed only starting materials to be present. Ishikawa et al.<sup>40</sup> reported the different activities of oven-dried and freeze-dried potassium fluoride. The fluorinating ability of potassium fluoride and caesium fluoride, which can generate the so-called "naked" fluoride ion is well known.<sup>41,42,44,96</sup> To account for the difference between the activities of oven-dried and freeze-dried potassium fluoride, phenol and p-nitrophenol were alkylated at about 60°C in DMF. In the alkylation reactions of phenol, about 10% fluorinated compound was obtained when oven-dried potassium fluoride was used. The main product, benzyl phenyl ether, was found to be less than that obtained by using freeze-dried potassium fluoride. It appeared that oven-dried potassium fluoride acts as a nucleophile as well as a hydrogen

bond electron donor. In the case of p-nitrophenol, no fluorinated compound was found, even when oven-dried potassium fluoride was used. The yield of ether was almost the same in both the reactions of p-nitrophenol where oven-dried and freeze-dried potassium fluoride were used. However the yield of the benzyl phenyl ether was different from the two sources of potassium fluoride. Yields were good, but not quantitative in the freeze-dried potassium fluoride system (cf. Table IV). To check whether the freeze-dried potassium fluoride contained hydrated salt or not, 3.50 g oven-dried potassium fluoride was dissolved in water to make a saturated solution. The solution was frozen in the freezer and dried on a vacuum line for four days. The final weight of the freeze-dried potassium fluoride was 3.51 g. Therefore, it was clear that freeze-dried potassium fluoride did not contain significant amounts of hydrated potassium fluoride.

From these observations, it was found that freeze-dried potassium fluoride was more effective as a hydrogen-bond forming catalytic reagent for alkylation of phenol. Calcine-dried potassium fluoride had a greater fluorinating ability than the freeze-dried salt. This difference did not apply in the alkylation reactions of p-nitrophenol. The reason may be that p-nitrophenol forms a stronger hydrogen bond with the fluoride ion, giving a faster reaction and thus consumption of benzyl halide before competing fluorination could occur. The identification of benzyl fluoride was done by  $^1\text{H}$  NMR (the benzylic proton's peak was a doublet centered at  $\delta = 5.35$  ppm, with coupling constant  $2J_{\text{HF}} = 48$  Hz) and GC/mass spectrometry. The percentage of benzyl fluoride was measured by integrating the benzylic

Table IV. Reactions of phenol and p-nitrophenol with benzyl bromide using oven-dried and freeze-dried potassium fluoride in DMF.

Phenols used	Potassium fluoride	Temperature	Time	Conversion*	Isolated Yield of ether
phenol	oven-dried	60°C	24 h	100%	67% ether 10% benzyl fluoride <sup>a</sup>
phenol	freeze-dried	60°C	24 h	100%	73%
p-nitrophenol	oven-dried	60°C	19 h	100%	76%
p-nitrophenol	freeze-dried	60°C	19 h	100%	76%

\*The percent of conversion was based on the percentage of benzyl halide consumed.

<sup>a</sup>The percentage of benzyl fluoride was measured by integration of the benzylic proton's peaks of the <sup>1</sup>H NMR spectrum.

proton's peak area of the ethereal extract of the reaction mixture. The mass spectrum is shown in the Appendix.

(B) Homogeneous reactions: For these reactions, tetrabutylammonium fluoride was used as the source of fluoride ion. Tetrabutylammonium fluoride is highly hygroscopic; to get it perfectly dry is rather difficult. The presence of water in the system changes the course of alkylation reactions of phenols. Phenol, when alkylated in toluene, produced a mixture of benzyl phenyl ether, benzyl alcohol and benzyl fluoride (cf. Table V). Tetrabutylammonium fluoride was found to be less soluble in toluene; the conversion was not 100% even at about 80°C up to 24 hours. In DMF, the reaction was observed to be complete within 75 hours at room temperature, but the products so formed were a mixture of benzyl phenyl ether, benzyl formate and benzyl fluoride. One reaction was run in the mixed solvent, benzene with 10% DMF. In this mixed solvent, fluorination was the major reaction. Comparing the three solvents, toluene, DMF and benzene/DMF, it was observed that change from nonpolar aprotic (toluene) to polar aprotic (DMF) also changed the course of fluoride assisted homogeneous reactions. In toluene, benzyl fluoride was the major product, but in DMF benzyl phenyl ether was the major product. It appeared that polar aprotic solvent favoured O-alkylation and nonpolar aprotic solvent favoured fluorination when the soluble tetrabutylammonium fluoride was used as the catalyst. The byproducts were benzyl alcohol and benzyl formate. It was quite reasonable that the trace amount of water present in the reaction mixture may hydrolyse benzyl bromide to benzyl alcohol.



Table V. Reactions of various phenols with benzyl bromide in the presence of tetrabutylammonium fluoride in various solvents. Homogeneous reactions.

Phenols used	Catalyst	Solvent	Temperature	Time	Conversion*	Product	Isolated Yield
phenol	tetrabutyl-ammonium fluoride	toluene	82°C	24 h	70%	ether benzyl alcohol benzyl fluoride	20% <sup>a</sup> 4% 76%
phenol	tetrabutyl-ammonium fluoride	DMF	23°C	75 h	100%	ether benzyl formate benzyl fluoride	54% <sup>a</sup> 6% 40%
phenol	tetrabutyl-ammonium fluoride	benzene with 10% DMF	70°C	24 h	100%	ether formate fluoride	15% <sup>a</sup> 5% 80%
p-nitrophenol	tetrabutyl-ammonium fluoride	DMF	23°C	24 h	100%	ether	76% <sup>b</sup>
p-nitrophenol	tetrabutyl-ammonium fluoride	benzene with 10% DMF	23°C	2 h	100%	ether	75% <sup>b</sup>
p-nitrophenol	tetrabutyl-ammonium fluoride	benzene with 25% DMF	23°C	1 h	100%	ether	75% <sup>b</sup>
2,6-ditertiarybutyl-4-methyl phenol	tetrabutyl-ammonium fluoride	toluene	82°C	24 h	100%	fluoride	
2,6-ditertiarybutyl-4-methyl phenol	tetrabutyl-ammonium fluoride	DMF	23°C	24 H	100%	formate fluoride mixture	8% 48% 44% <sup>c</sup>

\*The percent of conversion was based on the percentage of benzyl halide consumed.

<sup>a</sup>The yields were not isolated, but calculated from the integration of the <sup>1</sup>H NMR spectrum.

<sup>b</sup>The isolated yield.

<sup>c</sup>The mixture was not identified.

DMF can also be hydrolysed by water, producing formic acid and dimethyl amine.<sup>97</sup> The role of water in the alkylation reactions of phenol has been studied and described separately later on. However, in the mixed solvents, it was observed that there was a decrease in the percentage of ether as compared to the percentage of benzyl fluoride. It seemed that in benzene with 10% DMF, tetrabutylammonium fluoride was found to be a better fluorinating agent than it was in toluene. Benzyl formate was also formed in the mixed solvent. Phenol-fluoride monosolvate did not contain water, but the excess tetrabutylammonium fluoride did contain some. Therefore, it could be better to use anhydrous metallic fluoride instead of using tetrabutylammonium fluoride to avoid the interference of water.

In the alkylation of p-nitrophenol, both the mixed solvent and DMF were used as solvents. In benzene with 25% DMF, the time taken was one hour at room temperature for completion of the reaction, in benzene with 10% DMF, it was two hours, but in pure DMF the time was 24 hours. It was found quite surprising that the use of mixed solvent was more efficient than the polar solvent (DMF) for the alkylation of p-nitrophenol, using tetrabutylammonium fluoride as catalyst. Therefore the role of the solvent in this homogeneous reaction for the alkylation of p-nitrophenol was not very clear. There was no byproduct obtained in these p-nitrophenol alkylation reactions. Though there might be a possibility of having water in the excess tetrabutylammonium fluoride, the presence of these small amounts of water could not change the course of alkylation of p-nitrophenol, but it changed significantly in the alkylation of phenol. Therefore it

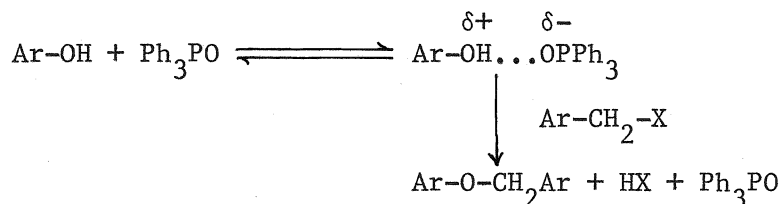
appeared that the hydrogen bonding of fluoride with p-nitrophenol was much stronger than that of fluoride with phenol.

Alkylation of 2,6-di-tert-butyl-4-methylphenol was also attempted using tetrabutylammonium fluoride in toluene and in DMF. In toluene, only benzyl fluoride was obtained, no alkylation took place. Thus in toluene, tetrabutylammonium fluoride acted as a good fluorinating agent in the alkylation reaction, especially when the sterically hindered phenol was present. In general, there was a competition between the fluorination and the alkylation reactions, and fluorination was faster than alkylation in nonpolar aprotic solvent versus the polar aprotic solvent. To assess the fluorinating ability of tetrabutylammonium fluoride in toluene, one reaction was run between benzyl bromide and tetrabutylammonium fluoride only. At room temperature, the fluorination was very small even after six days. When the reaction mixture was heated to about 82°C for 24 hours, 100% conversion was obtained. Thus, tetrabutylammonium fluoride was found to be a good fluorinating agent in toluene, if the potential nucleophile is highly hindered. Also in DMF, no alkylated product was formed in the alkylation reaction of the sterically hindered phenol. A mixture of products was found, of which benzyl fluoride was the major one identified. Benzyl formate was found as one of the products in small quantities. Besides these, some other products were also found to be formed in small quantities which could not be well separated and remained unidentified. Therefore, for highly sterically hindered phenols such as 2,6-di-tert-butyl-4-methylphenol, alkylation was not possible even by using tetrabutylammonium fluoride in either polar or nonpolar aprotic solvents.

#### 4.4 Attempted alkylation reactions of phenols in the presence of triphenylphosphine oxide:

In these reactions, we attempted to alkylate phenol and p-nitrophenol using triphenylphosphine oxide as hydrogen bond assisted catalyst. The solvents used were toluene and DMF. The reactions were not successful, i.e., no alkylated product was obtained in any reaction either in toluene or in DMF. From these reactions, it was observed that triphenylphosphine oxide may not be a good hydrogen bond electron donor.

To verify the hydrogen bonding between phenol and triphenylphosphine oxide,  $^1\text{H}$  NMR studies were carried out at ambient temperature (cf. Table VI and Figure 1). These studies showed that there is hydrogen bonding between phenol and triphenylphosphine oxide. The hydrogen bond becomes limiting after a 1:1 mole ratio of phenol and triphenylphosphine oxide. To compare the hydrogen bonding of the polar solvent  $\text{CDCl}_3$  and the phenol as well as the intermolecular hydrogen bonding of phenol, another set of experiments was done in the nonpolar solvents. However, there was no doubt about the hydrogen bonding of triphenylphosphine oxide with phenols, but this hydrogen bonding did not assist the alkylation reaction. The expected reaction was:



The first stage has been verified by  $^1\text{H}$  NMR studies, that there is hydrogen bonding between phenol and triphenylphosphine oxide. To account for the inability of the second stage, it may be mentioned that there is no place

Table VI. Hydroxy proton chemical shifts of 1M solutions of phenol with triphenylphosphine oxide in  $\text{CDCl}_3$ .

Mole ratio of phenol and triphenylphosphine oxide	$\delta(\text{OH})$ observed in ppm
1:0	5.83
1:0.125	6.6
1:0.25	7.4
1:0.5	8.73
1:1	9.75
1:2	10.29
1:3	10.46
1:4	10.56
1:5	10.66

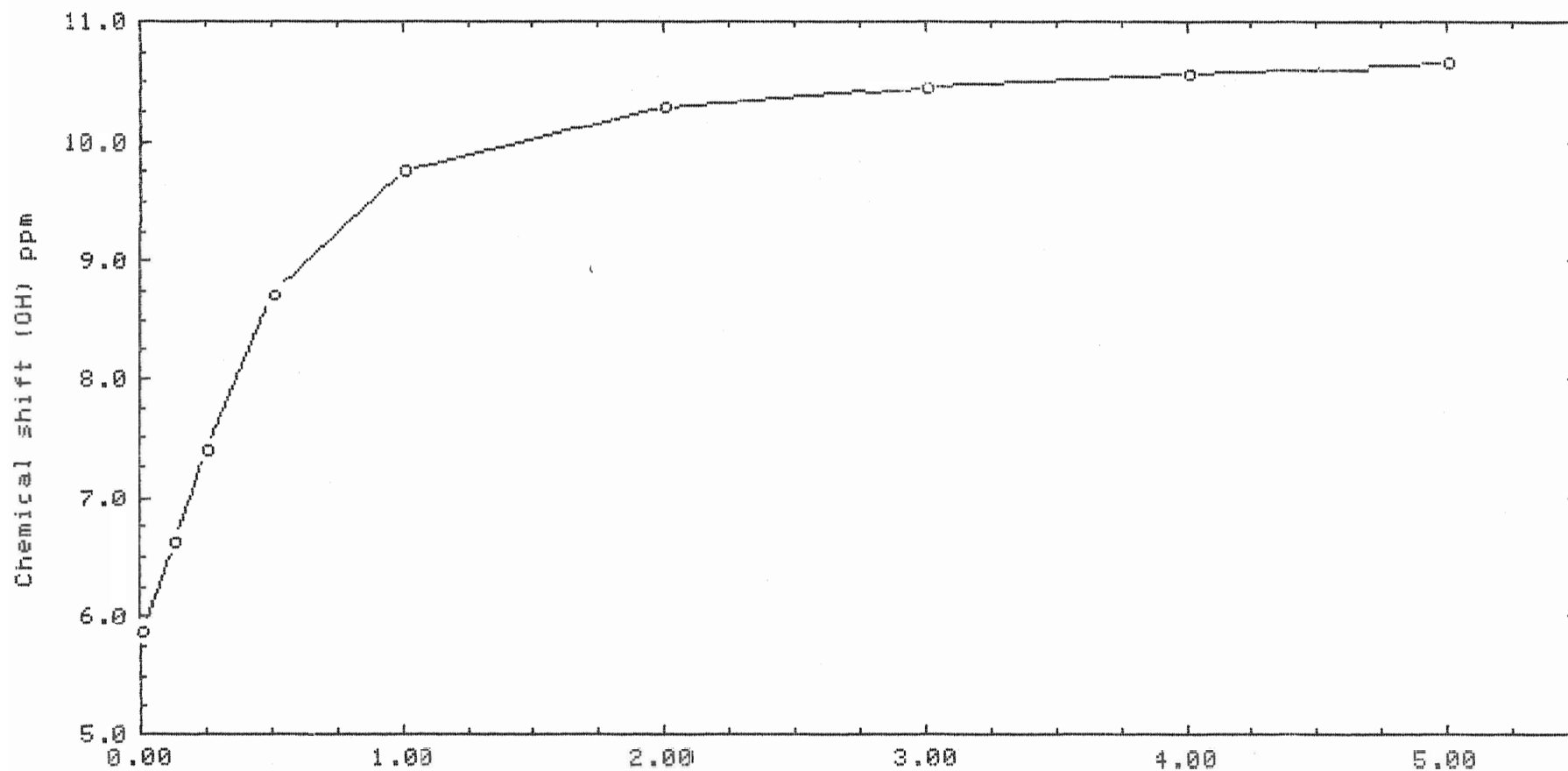


Figure 1. Plot of  $\delta(\text{OH})$  of phenol versus the mole ratio of triphenylphosphine oxide with phenol

Table VII. Hydroxy proton chemical shift of phenol in various solvents at various concentrations.

Molarity	Solvent	$\delta$ in ppm
0.05 M	hexane	not observed
0.1 M	hexane	4.78
0.25 M	hexane	5.35
0.5 M	hexane	6.00
1 M	hexane	6.63
0.05 M	$\text{CCl}_4$	4.46
0.1 M	$\text{CCl}_4$	4.78
0.25 M	$\text{CCl}_4$	5.30
0.5 M	$\text{CCl}_4$	5.95
1 M	$\text{CCl}_4$	6.46
0.05 M	$\text{CDCl}_3$	4.78
0.1 M	$\text{CDCl}_3$	4.85
0.25 M	$\text{CDCl}_3$	5.15
0.5 M	$\text{CDCl}_3$	5.65
1 M	$\text{CDCl}_3$	5.83

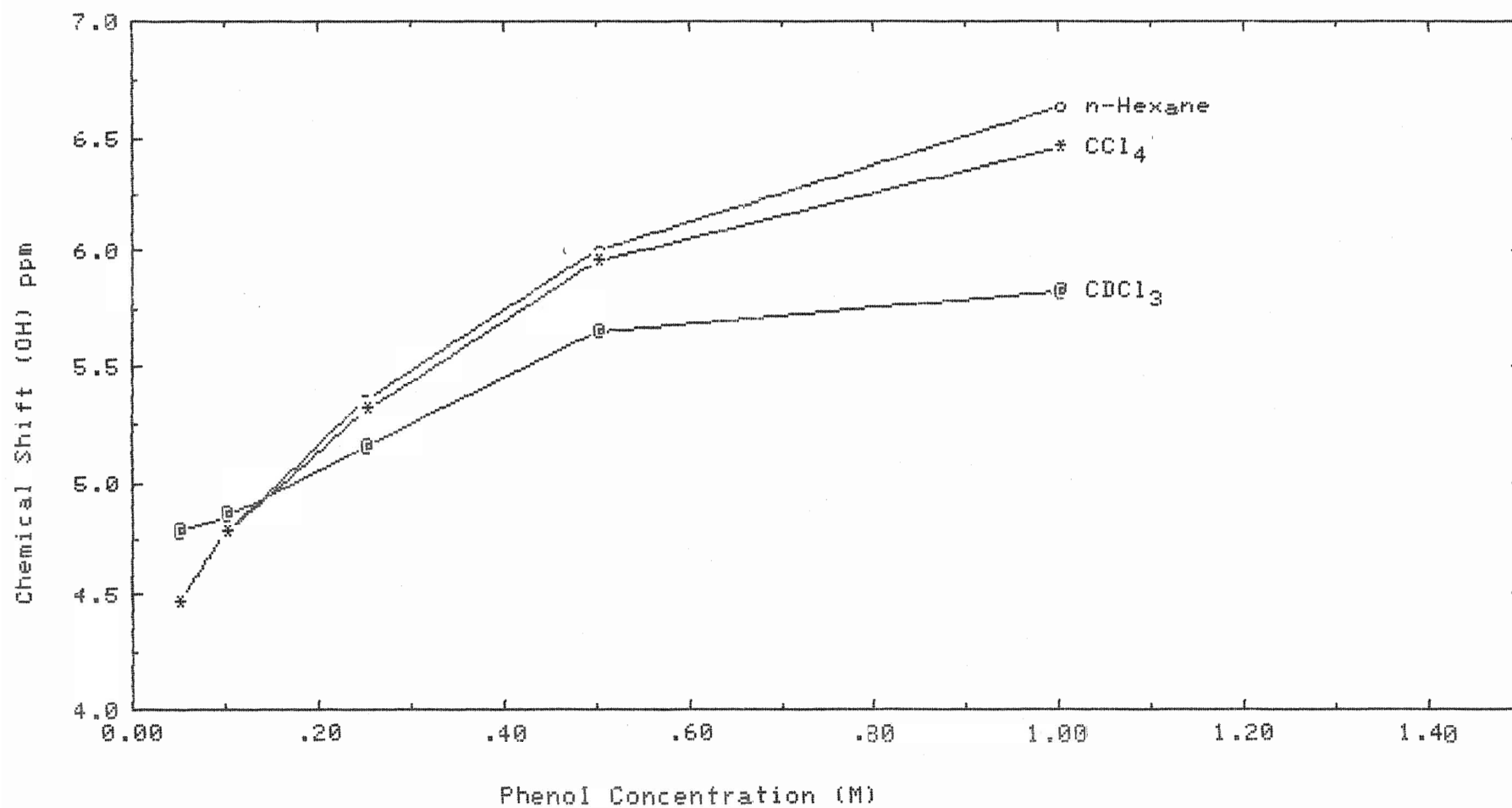
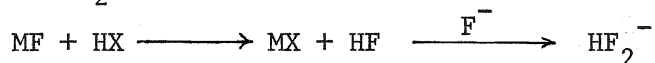


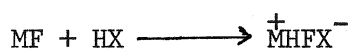
Figure 2. Plot of  $\delta(\text{OH})$  of phenol versus molarity in various solvents



for the hydrogen halide to go. If we compare with the fluoride assisted reactions, the hydrogen halide was picked up by metal fluoride to produce hydrogen fluoride which reacts with fluoride ion to produce the stable species  $\text{HF}_2^-$ .<sup>98</sup>



or



Under other conditions, triphenylphosphine oxide may be a good catalyst for hydrogen bond assisted reactions, e.g., in the traditionally base-catalysed reaction.

#### 4.5 Use of fluoride ion with a phase transfer catalyst:

An attempt was made by Miller and Demmig<sup>99</sup> to use fluoride ion with a phase transfer catalyst for the alkylation of 2-naphthol. The reaction was run in a DMF and water mixture containing potassium fluoride. The experiment was unsuccessful. As an extension of that work, detailed studies were made by using solid potassium fluoride and tetrabutylammonium bromide in DMF in the alkylation reactions of phenol. These reactions, when carried out under anhydrous conditions, gave good results. In these reactions, benzyl chloride was used as the alkylating agent. At about 100°C, the normal time required for the completion of the reaction was 19 hours without using the phase transfer catalyst. When tetrabutylammonium bromide was used in the reaction, it was completed within four hours, having the same yield (cf. Table VIII). The yield in these reactions, especially at high temperature, was found to be quite low. The optimum temperature was

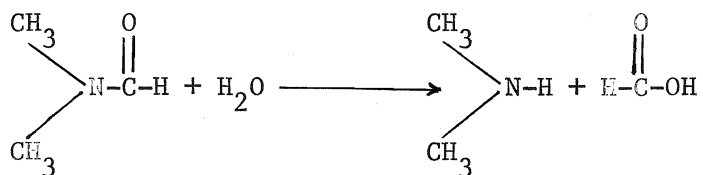
Table VIII. Reactions of phenol with benzyl chloride in the presence of potassium fluoride and tetrabutylammonium bromide in DMF.

Amount of phenol	Amount of benzyl chloride	Amount of potassium fluoride	Amount of tetrabutyl- ammonium bromide	Time at 100°C	Product with yield (isolated)
0.01 mole	0.01 mole	0.02 mole	0.02 mole	5½ h	ether 59%
0.01 mole	0.01 mole	0.02 mole	0.01 mole	4½ h	ether 58%
0.01 mole	0.01 mole	0.02 mole	0.005 mole	4½ h	ether 63%
0.01 mole	0.01 mole	0.02 mole	0.002 mole	4 h	ether 62%
0.01 mole	0.01 mole	0.02 mole	0.001 mole	4½ h	ether 63%
0.01 mole	0.01 mole	0.02 mole	0.0004 mole	8½ h	ether 60%
0.01 mole	0.01 mole	0.02 mole	0.0002 mole	9½ h	ether 61%

between 60°C and 70°C. The amount of the phase transfer catalyst used in the mole ratio was 0.001 mole (one tenth of the reactants) and was quite sufficient for the reaction to occur. Thus, fluoride ion from solid potassium fluoride can be transferred to the solution via a phase transfer catalyst to enhance the alkylation reaction of phenol. This was found in contrast with the homogeneous reactions for the alkylation of phenol, where the soluble tetrabutylammonium fluoride acts as a fluorinating agent as well. However, it may be suggested that, for the alkylation of phenol using fluoride ion, it is better to use the phase transfer catalyst and potassium fluoride rather than the tetraalkylammonium fluoride, which is very difficult to dry.

#### 4.6 Influence of water in the alkylation reaction of phenol:

In the beginning of this research, when a reaction was run in DMF, a small amount of benzyl formate was produced, and the yield of ether was relatively low. The formation of benzyl formate was surprising. It was found in the literature<sup>97</sup> that DMF can be hydrolysed readily to produce formic acid and dimethyl amine.



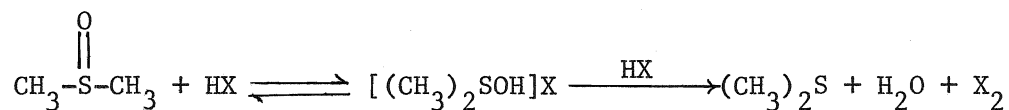
Once formic acid is produced, it forms a hydrogen bond with fluoride ion and thus produces the benzyl formate. Therefore that reaction was not carried out under anhydrous conditions. This observation encouraged us to study the role of water in the alkylation reaction of phenol. It is also known

that the presence of water may have a profound effect on the basic behaviour of the fluoride anion.<sup>100-103</sup> In the absence of a more powerful hydrogen bond electron acceptor, water solvates the fluoride anion and masks it. Ogilvie et al.<sup>104</sup> have shown that when fluoride ion is faced with two possible reaction centres, it preferentially attacks the one closest to the hydroxyl group. In this part of our work, the tolerance for water in the alkylation reaction of phenol has been measured. When the reactions were run in the presence of water, the major byproduct was benzyl formate. To confirm the formation of benzyl formate, one reaction of benzyl bromide with formic acid was run at about 70°C, in the presence of potassium fluoride in DMF. The reaction was found to be completed within 1½ hours and the product was 100% benzyl formate. The compound was identified by <sup>1</sup>H NMR and mass spectrometry.

<sup>1</sup>H NMR:  $\delta$  = 5.21 ppm (s, 2H) 7.41 ppm (s, 5H) and 8.15 ppm (s, 1H). The molecular ion was at m/z 136 (M<sup>+</sup>). When one reaction was run in DMSO in the presence of water, no benzyl formate was produced. Therefore, it may be said that the water in the reaction mixture easily hydrolyses the solvent DMF, producing formic acid. Formic acid is more acidic than phenol, therefore it forms a much stronger hydrogen bond with the fluoride ion, and thus competes with the phenol for alkylation. As the amount of water was increased, the formation of benzyl formate was increased with a decrease of the ether formation. Besides the benzyl formate, there were other products in very small quantities. One compound was identified as benzyl fluoride, the other as benzaldehyde, and some other fractions were present. These fractions could not be separated, and remained unidentified.

However, from the studies above, it was observed that a remarkable amount of water may be present without completely suppressing ether formation (cf. Table IX).

To study the action of water with benzyl bromide, one reaction was run in DMSO in the presence of potassium fluoride. The reaction was found to be completed after 12 hours at about 70°C. The products were analysed by GC/mass spectrometry. Four products were obtained: (i) benzyl fluoride, (ii) benzaldehyde, (iii) benzyl alcohol, and (iv) benzylmethyl sulfide. Abdul Aziz and Clark<sup>81</sup> have already mentioned that benzyl bromide is hydrolysed by water, when treated in aqueous DMSO in the presence of fluoride ion, producing benzyl alcohol. In our reaction, benzyl alcohol was found in very small quantities, but benzaldehyde and benzylmethyl sulfide were formed in significant amounts. It appeared that the expected benzyl alcohol is oxidised to benzaldehyde. It has been mentioned in the literature<sup>105</sup> that dimethyl sulfoxide can be used as an oxidising agent. Thus the formation of benzaldehyde can be explained as the oxidation of benzyl alcohol by DMSO. It has also been reported<sup>105</sup> that in aqueous solutions of hydrogen halide, HX (e.g., HBr), dimethyl sulfoxide can be reduced to dimethyl sulfide.

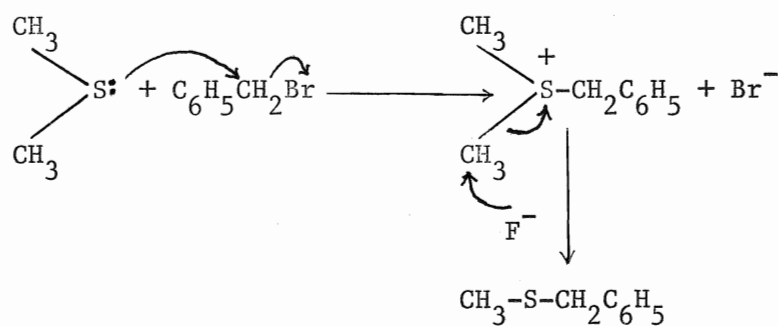


The dimethyl sulfide thus formed during the above reaction may act as a nucleophile to form sulfonium salt, which in the presence of fluoride may form benzylmethyl sulfide, according to the following reaction.

Table IX. Reactions of phenol with benzyl bromide in the presence of water in DMF using potassium fluoride.

Phenol and benzyl bromide	Solvent	Potassium fluoride	Water	Temperature	Time	Conversion*	Identified product	Yield isolated (ether)
0.01 mole	DMF	0.02 mole	0.01 mole	80°C	2 h	100%	ether fluoride formate	33%
0.01 mole	DMF	0.02 mole	0.015 mole	80°C	2 h	100%	ether fluoride formate	31%
0.01 mole	DMF	0.02 mole	0.02 mole	80°C	2½ h	100%	ether fluoride formate	33%
0.01 mole	DMF	0.02 mole	0.03 mole	80°C	2½ h	95%	ether fluoride formate	33%
0.01 mole	DMF	0.02 mole	0.04 mole	80°C	3 h	100%	ether fluoride formate	34%
0.01 mole	DMF	0.02 mole	0.05 mole	80°C	3¼ h	95%	ether fluoride formate	30%
0.01 mole	DMF	0.02 mole	0.06 mole	80°C	3½ h	95%	ether fluoride formate	22%
0.01 mole	DMF	0.02 mole	0.1 mole	80°C	6 h	100%	ether fluoride formate	0.0%

\*The percent of conversion was based on the percentage of benzyl halide consumed.



Therefore, it was observed that the presence of water in the alkylation reactions of phenols changes the course of the reaction drastically.

## Chapter 5

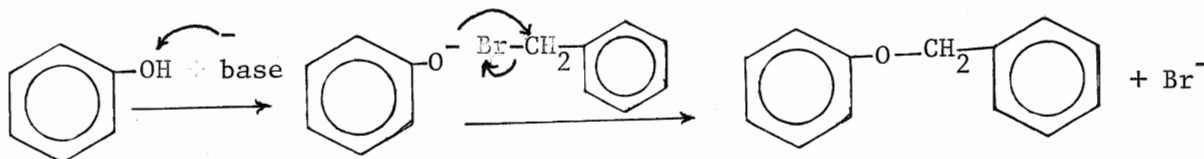
### GENERAL DISCUSSION AND CONCLUSION

5.1 Now it is well known that fluoride ion assisted reactions are considered as hydrogen bond assisted reactions. From this research, it also appears that hydrogen bond assisted reactions are better methods than the conventional base assisted reactions for the alkylation of phenols. However, the choice of fluoride and solvents is important in determining the course and rate of the reaction. Even when the same potassium fluoride was used in this research, the different ways of drying it gave different results. Oven dried potassium fluoride gave some fluorinated compounds, but freeze-dried potassium fluoride gave no fluorinated product, therefore more alkylated product was obtained. The cause of different activities of oven-dried and freeze-dried potassium fluoride is not known. It was reported<sup>106,107</sup> that freeze-dried potassium fluoride is less hygroscopic than oven-dried potassium fluoride. It is also known that the presence of water may have a profound effect on the basic behaviour of fluoride anion.<sup>100-103</sup> Tetrabutylammonium fluoride is more soluble in organic solvents, producing more free fluoride ion and hence an increase in the rate of the reaction, but the behaviour of fluoride ion depends on the dielectric constant of the solvent. In a nonpolar aprotic solvent, the fluoride ion (soluble) acts as fluorinating agent as well, but in a polar aprotic solvent it acts as a hydrogen bonded complex only.

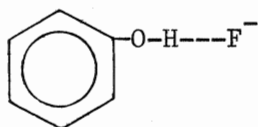


## 5.2 Mechanism of the reactions;

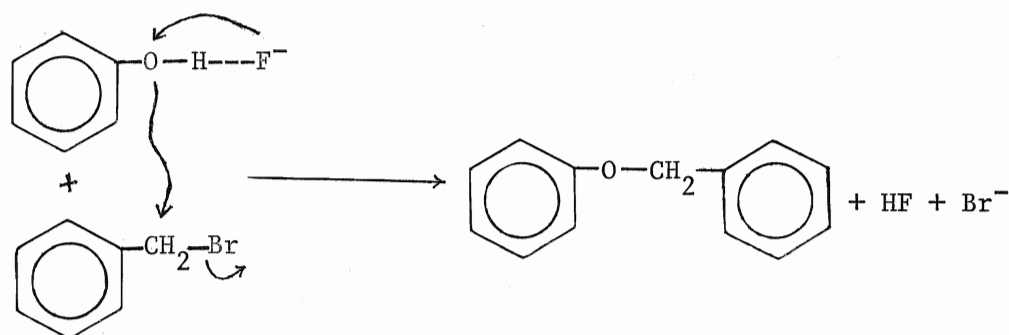
The mechanisms of the base assisted and hydrogen bond assisted reactions are slightly different. In the presence of a strong base, the acidic proton of the phenols is abstracted by the base, generating phenoxide ion. This phenoxide ion reacts with the alkylating agent as a nucleophile by an  $S_N2$  mechanism.



In the fluoride assisted reactions, the fluoride anion forms hydrogen bonds with the acidic proton of phenols, thereby producing a highly reactive anionic complex.



The anionic complex is quite stable and the formation of a hydrogen bond between the fluoride anion and the phenol resulted in the transfer of electron density from the anion to the organic part, thus enhancing the nucleophilicity of the organic species, while at the same time the nucleophilicity of the fluoride is reduced. The anionic complex reacts with the alkylating agents by an  $S_N2$  type mechanism.



In comparison between phenol and p-nitrophenol, it is quite evident that the more acidic the protic compound (phenols), the stronger the hydrogen bond shall be. The stronger hydrogen bonded complexes are more reactive. The stronger the hydrogen bond, the more transfer of the electron density on to the atom next to the acidic hydrogen atom, i.e., oxygen of the phenol.

### 5.3 Effects of solvents:

The solvents like DMF and DMSO are especially effective at solvating cations.<sup>32</sup> Thus in base assisted reactions, it was observed that the polar aprotic solvent such as DMF effectively solvates the cation, thereby producing more dissociated anion. The nonpolar aprotic solvent like toluene was found unable to solvate the cation, but the use of crown ether such as 18-crown-6 helped the solvation of the cation producing phenoxide ion in solution. Thus only O-alkylated products were found. It may be suggested that there was no contact ion pair which usually favours C-alkylation.

In fluoride assisted reactions, the polar aprotic solvent, DMF, solvates the cation more effectively, and as a result, the hydrogen bonded anionic complex was formed, which favoured O-alkylation. In nonpolar aprotic solvents, e.g., toluene, the reaction is thought to be occurring on the surface of the suspended potassium fluoride, i.e., the reaction was absolutely in the heterogeneous condition. The electronegative oxygen atom was not free to attack the alkylating agent. It may be suggested from our observation that for the alkylation of phenol in toluene using potassium fluoride, the electron density was completely delocalised in the ring, giving C-alkylated products only. However, for soluble fluorides such as tetrabutylammonium fluoride, the polar aprotic solvent favoured O-alkylation and a nonpolar aprotic solvent favoured fluorination. When a protic solvent was used in the alkylation reaction, it formed a hydrogen bond with the oxygen atom of the phenol, thus the oxygen atom becomes shielded, and as a result, C-alkylated products were formed.<sup>33</sup>

Though the solvent can control the course and rate of alkylation of phenols, the hydrogen bond plays an important role. If the hydrogen bond is very strong, activities of solvent become less effective. For example, in this research p-nitrophenol in benzene/DMF in the presence of oven-dried potassium fluoride gave only O-alkylated product, whereas phenol gave O-alkylated and fluorinated products under the same conditions. It appears that the p-nitrophenol-fluoride hydrogen bond is much stronger than the phenol-fluoride hydrogen bond, which controls the course of the reaction.

#### 5.4 Conclusion

To sum up, the above results indicate that hydrogen bonding is very important in the course and rate of phenol's alkylations. Protic solvents form hydrogen bonds with the electronegative oxygen atom of phenols, producing C-alkylation,<sup>33</sup> where the electron density is delocalised to the ring. An aprotic polar solvent favours O-alkylation and a nonpolar aprotic solvent favours C-alkylation, but if there is strong hydrogen bonding in the phenol-fluoride complex, it favours O-alkylation. The localisation of the negative charge depends on the strength of the hydrogen bonding, usually electron density being greater on the atom next to the hydrogen of the fluoride hydrogen bonded complex. Regarding fluoride ions, oven-dried potassium fluoride is a better fluorinating agent than freeze-dried potassium fluoride. The more soluble and reactive fluoride such as tetrabutylammonium fluoride is a better fluorinating agent in a nonpolar aprotic solvent, and a better hydrogen bonding agent in a polar aprotic solvent. Potassium fluoride can be used with a phase transfer catalyst in fluoride assisted organic synthesis, by using tetraalkylammonium halides other than fluoride under anhydrous conditions. The presence of water in the reaction plays a very important role. It decreases the main product ether, drastically. It can hydrolyse the solvent, DMF, to produce formic acid, which competes with phenol in the alkylation. It can hydrolyse the alkylating agent, producing the corresponding alcohol, which can be oxidised by an oxidising agent, e.g., DMSO. Water also helps to reduce the DMSO at the same time in the presence of hydrogen halide (e.g., HBr).

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## Appendix

DS-55 MASS INTENSITY REPORT:  
BALD16.1 [TIC=1189440, 100%=525552] EI

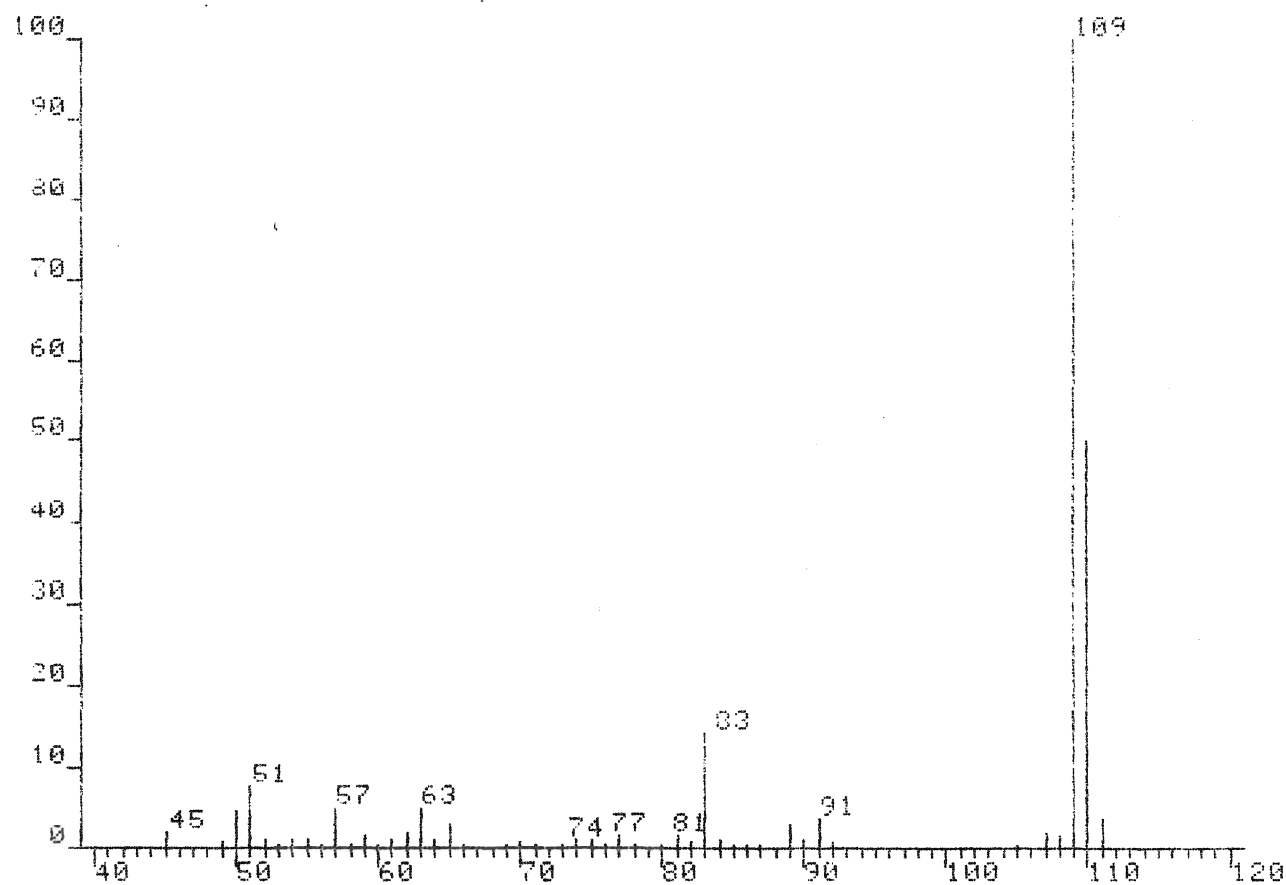


Figure A1. The mass spectrum of benzyl fluoride.

DS-55 MASS INTENSITY REPORT:  
BALD58.1 [TIC=791360, 100%=520080] EI

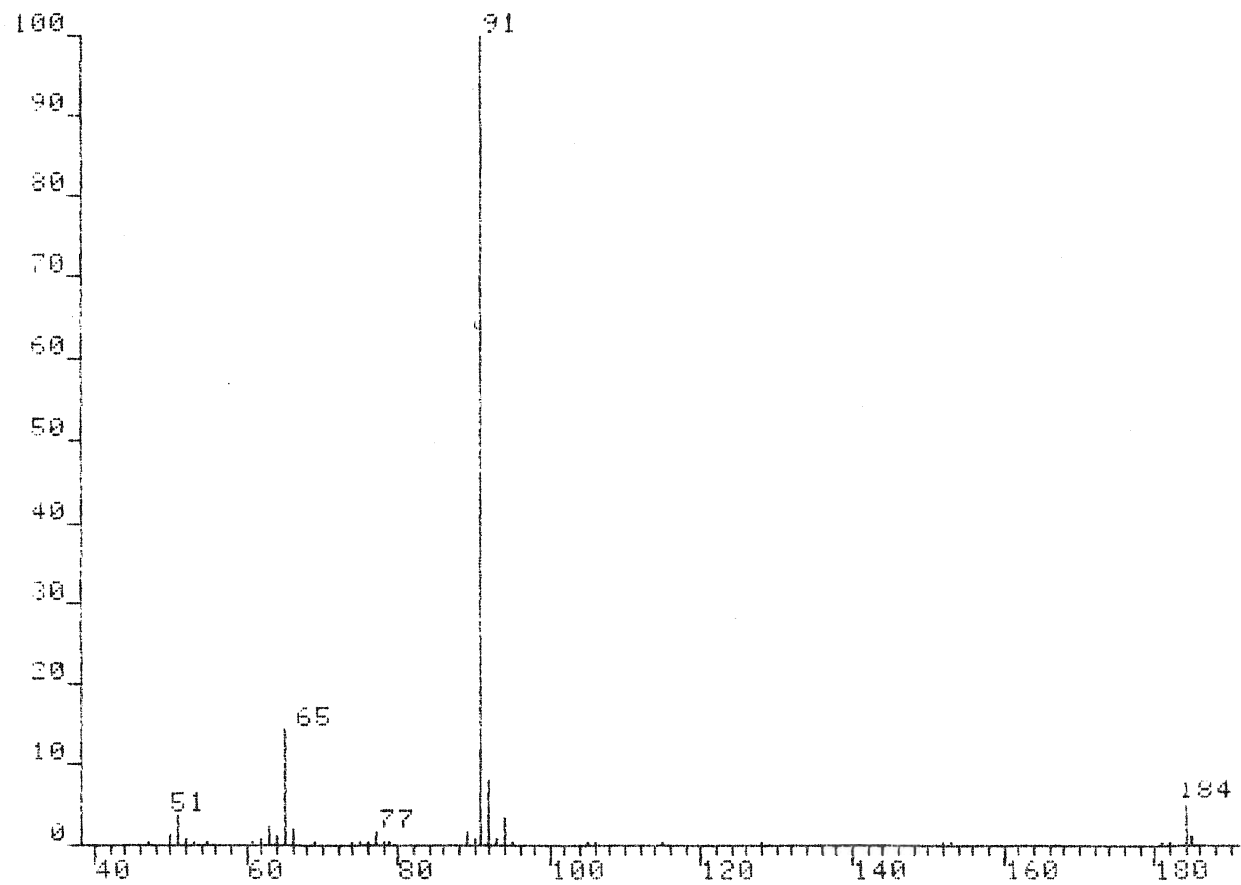


Figure A2. The mass spectrum of benzyl phenyl ether.

DS-55 MASS INTENSITY REPORT:  
1ALD72.1 [TIC=1437312, 100%=240268] EI

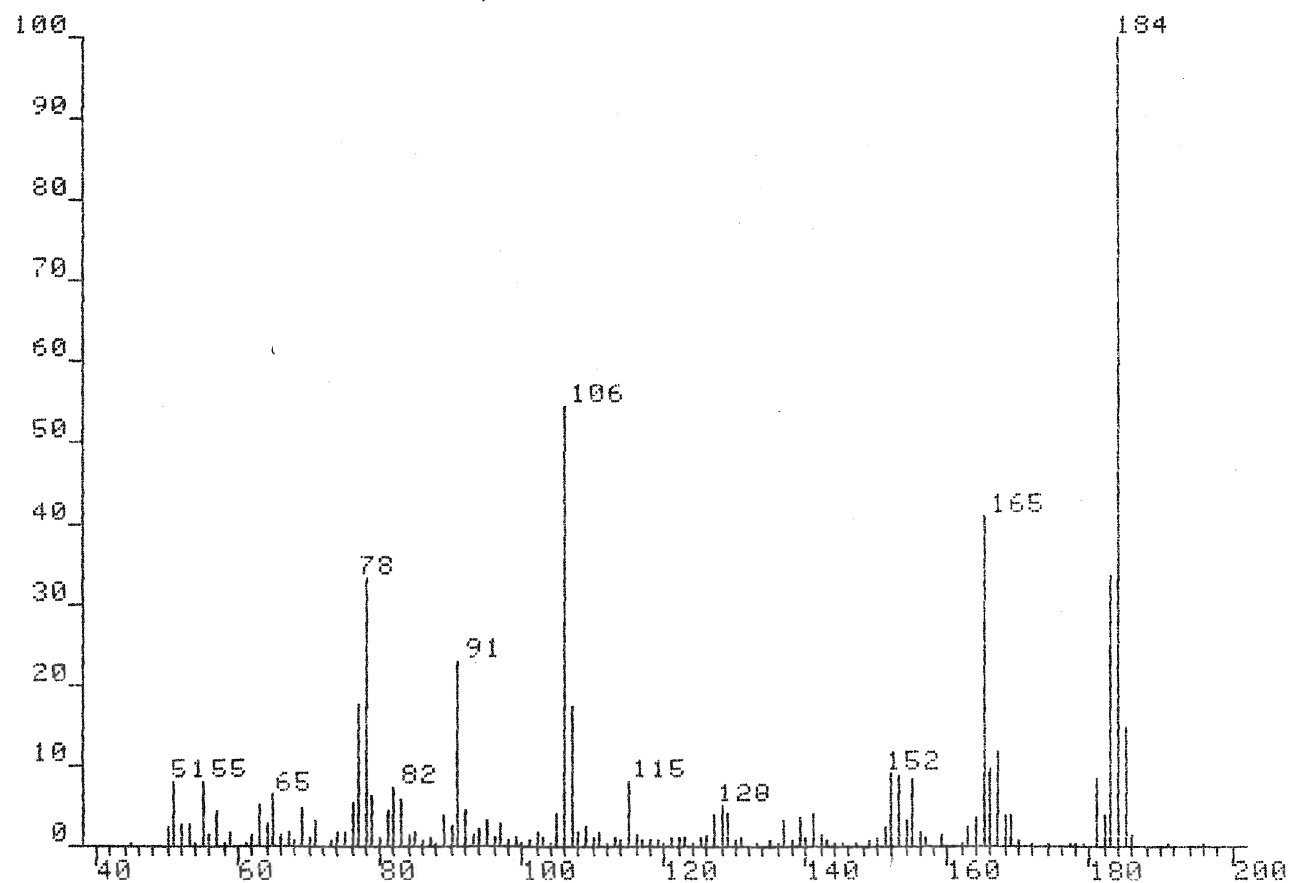


Figure A3. The mass spectrum of 2-benzyl phenol.

DS-55 MASS INTENSITY REPORT:  
1ALD75.1 [TIC=1963136, 100%=349264] EI

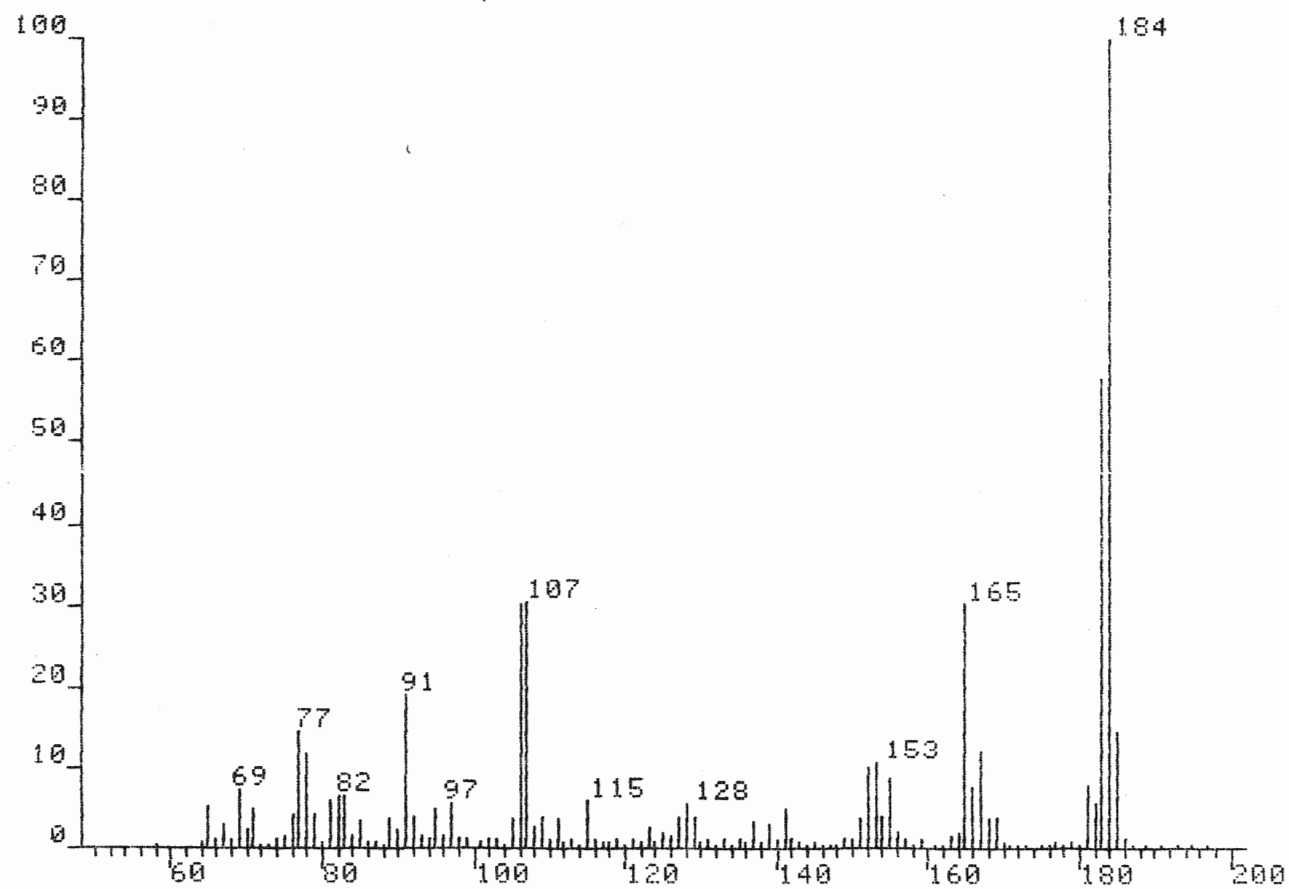


Figure A4. The mass spectrum of 4-benzyl phenol.



DS-55 MASS INTENSITY REPORT:  
1ALUD.65 [TIC=446976, 100%=52453] EI

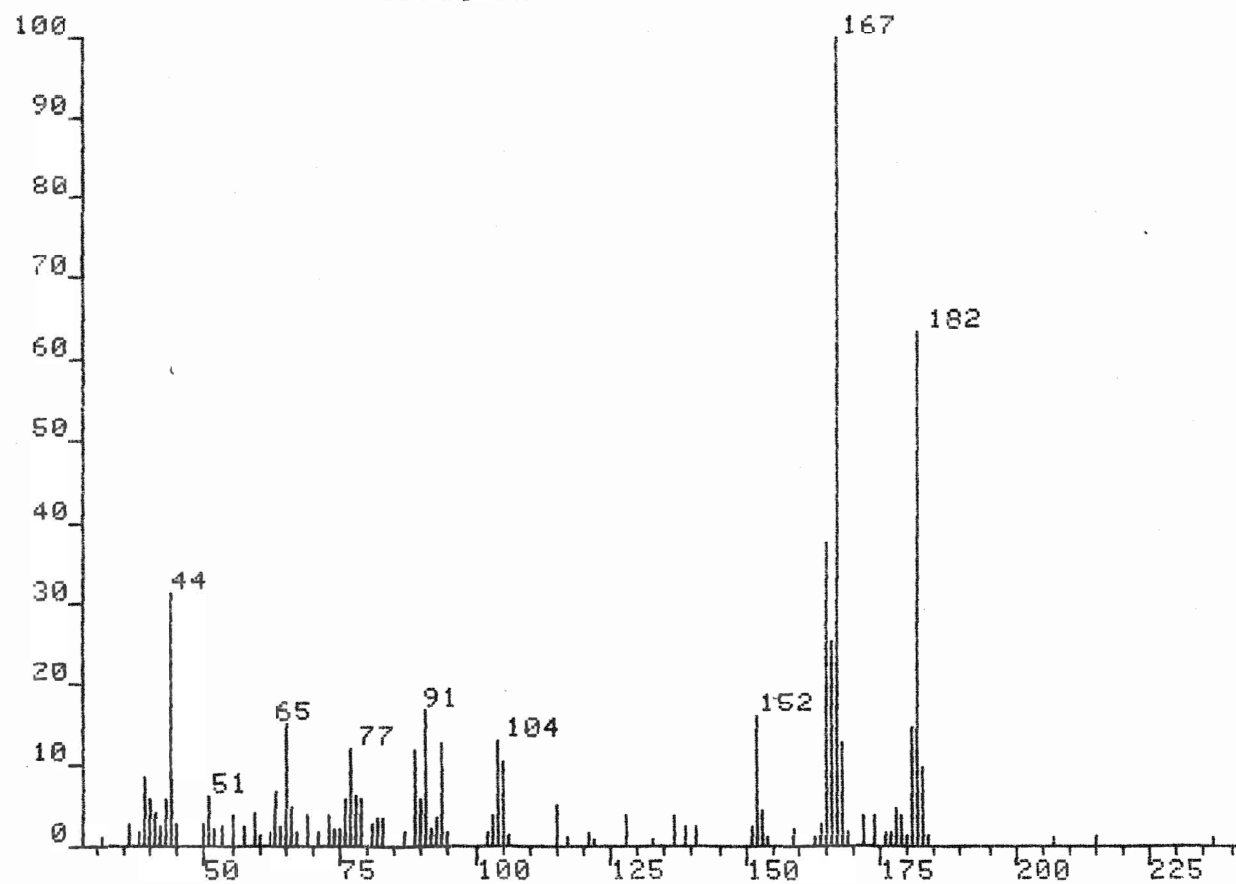


Figure A5. Mass spectrum of 2,2'-dimethylbiphenyl or 2,4'-dimethylbiphenyl.

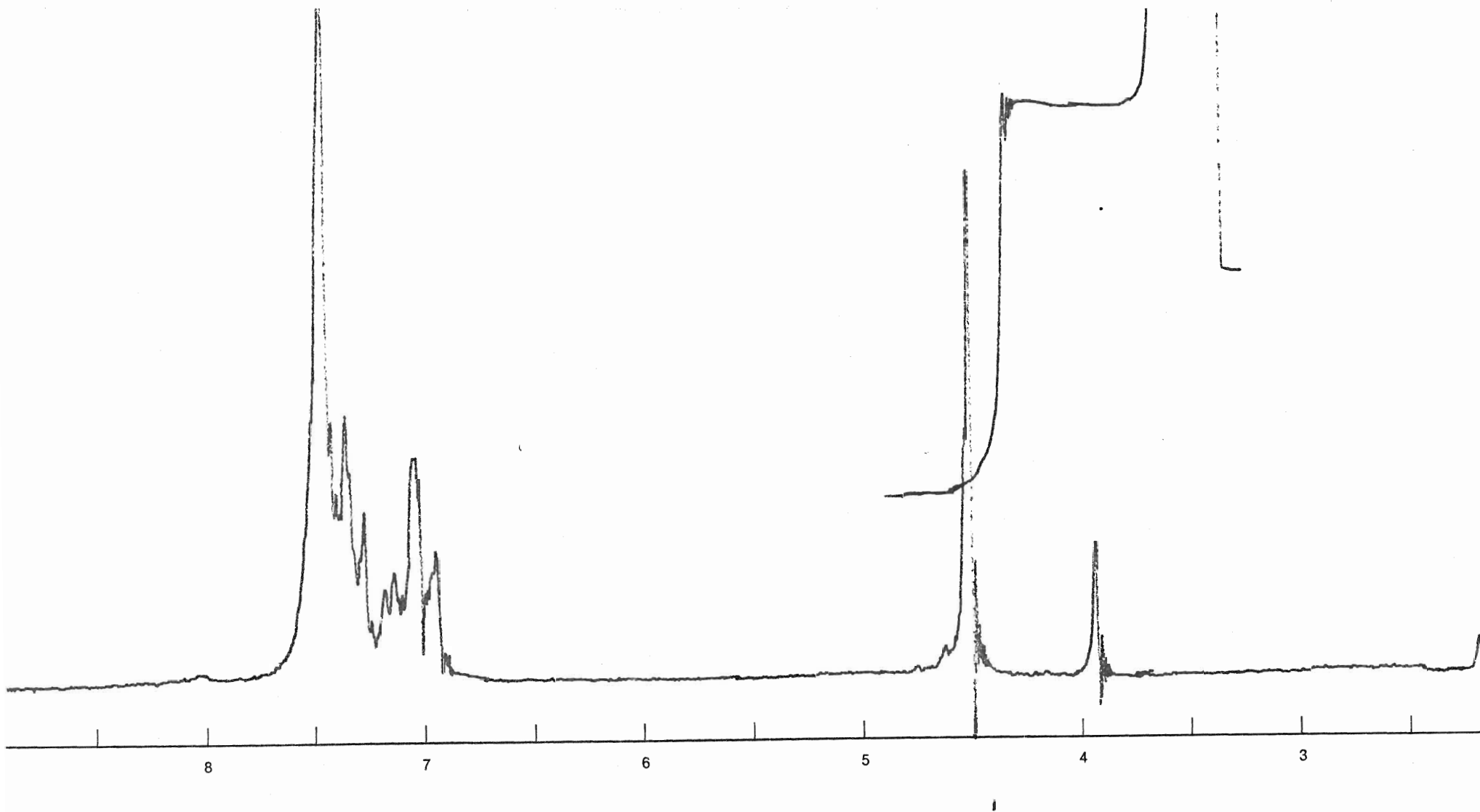


Figure A6. The  $^1\text{H}$  NMR spectrum of the reaction mixture of phenol with benzyl bromide in toluene in the presence of KF.