# SELECTIVE PARA-FUNCTIONALIZATION OF PHENOL

by

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# SUMMARY

In previous work done in our laboratories, a method was discovered to produce phenolic mono-ethers from 4-hydroxyacetophenone and other 4-hydroxyketones by treating with ammonium peroxy-disulfate in an alcohol as a reaction solvent and in the presence of concentrated sulphuric acid or other strong protonic acids. Since this method of producing 4-alkoxyphenol ethers provides a very convenient way to modify hydroquinone and substituted hydroquinones to produce a variety of phenol mono-ethers, it was of interest to study the general scope of this reaction, including a more detailed investigation of the reaction mechanism. In previous studies, it was suggested that interaction between the aromatic pi-system of hydroquinone and the cyclohexa-2,5-diene structure of benzoquinone plays a significant role during the reaction. It was therefore of interest to investigate whether other compounds that are also capable of forming the cyclohexa-2,5-diene structure, will interact in a manner analogous to the hydroquinone/benzoquinone couple. Two specific compounds were selected for this purpose, namely 4-nitrosophenol and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one .

The scope of etherification reactions of hydroquinone-benzoquinone or hydroquinone/benzoquinone like substrates such as 4-nitrosophenol and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one in the presence of acid catalyst and alcohols was investigated. These studies showed that hydroquinone, 4-nitrosophenol and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one successfully affords the phenolic ethers in good to excellent yield. For example, quantitative yield of 4-methoxyphenol could be obtained from a 1:1 mixture of hydroquinone and benzoquinone at the reflux temperature of methanol.

In order to study the reaction mechanism, the cross-over reaction between *tert*-butylhydroquinone and benzoquinone (or hydroquinone and *tert*-butylbenzoquinone) was studied in detail. The results of these cross-over reactions were used to propose a mechanistic pathway that could explain the requirement for

pi-interaction between the hydroquinone and benzoquinone molecules, the role of the acid catalyst, as well as the relative rates of hydroquinone and benzoquinone consumption during these reactions. The mechanism was also capable of explaining all the reaction products observed during these reactions.

The work was then extended to reactions of 4-nitrosophenol and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one with methanol in the presence of either hydroquinone or benzoquinone. The results of these investigations strongly suggest the presence of similar interactions between these molecules that also influence the outcome of the reactions.

The exploitation of pi-interactions between two molecules of these types investigated during this work opens an interesting field of chemistry. Clearly, the level of understanding developed during this work is only beginning to address this interesting field of chemistry and much work will need to be done to gain a fuller understanding of the chemistry involved as well as the potential synthetic value of these interactions.

**KEYWORDS**

**4-Alkoxypenol, 4-Methoxyphenol, Hydroquinone, 4-Nitrosophenol, 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one, Selective Substitution**

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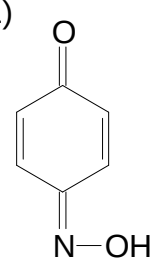


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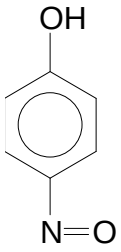


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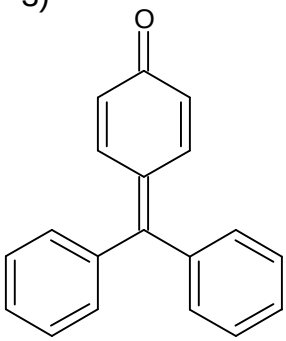


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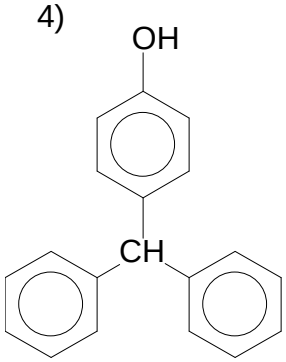


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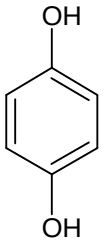


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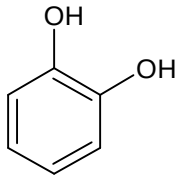


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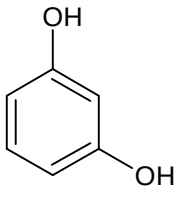


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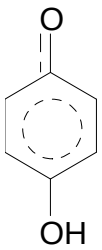

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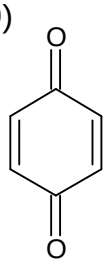


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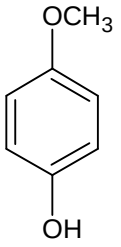


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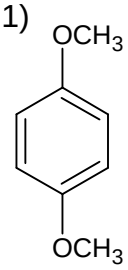


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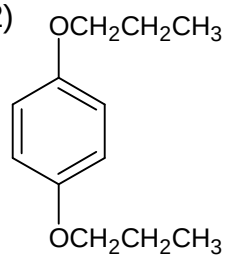


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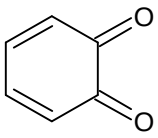


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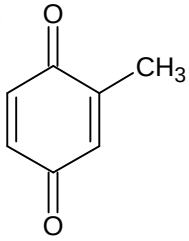


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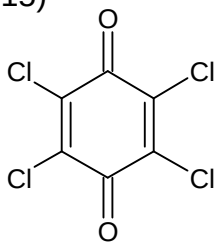


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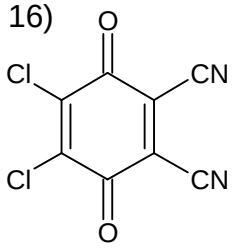


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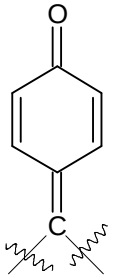


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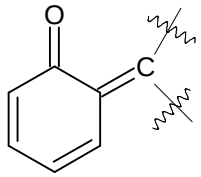

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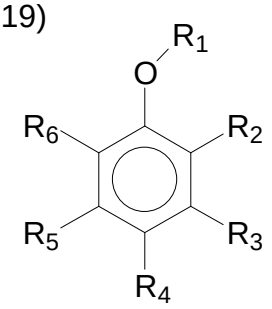


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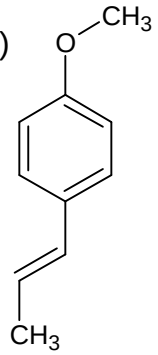


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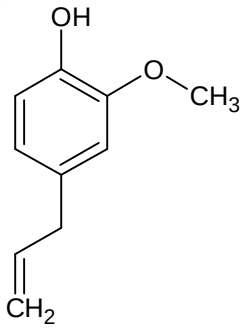


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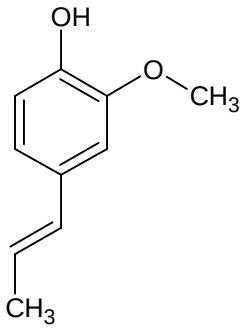


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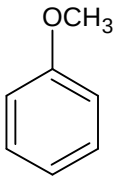


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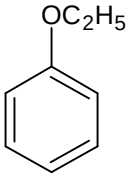


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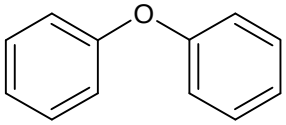


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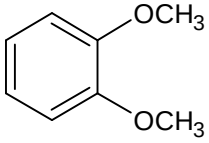


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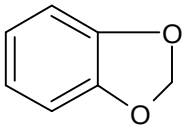


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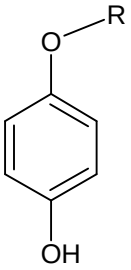

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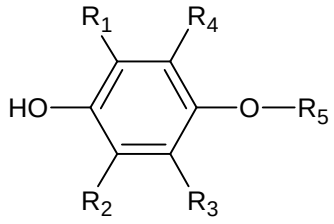


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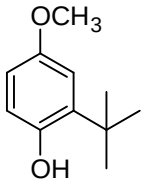


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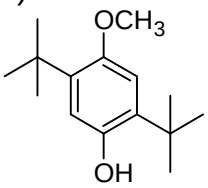


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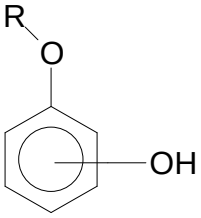


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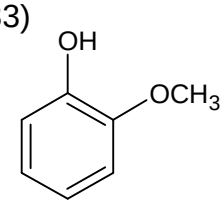


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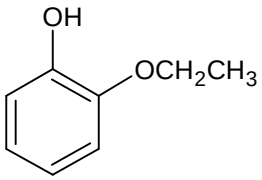


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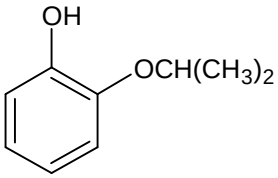


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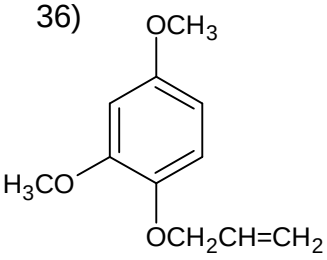


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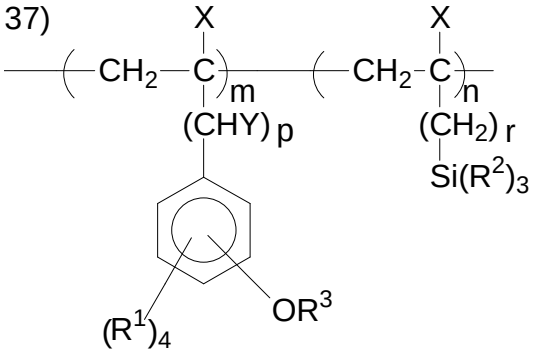


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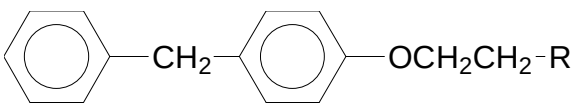

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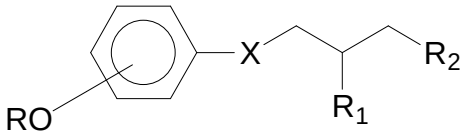


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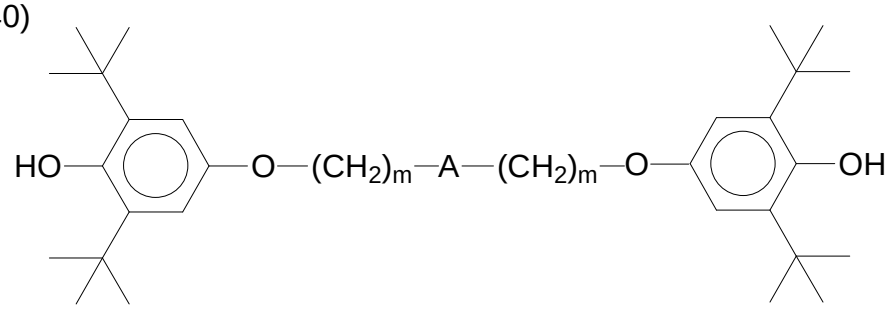


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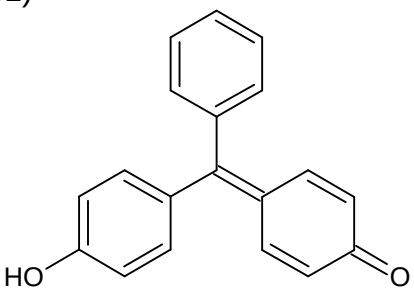


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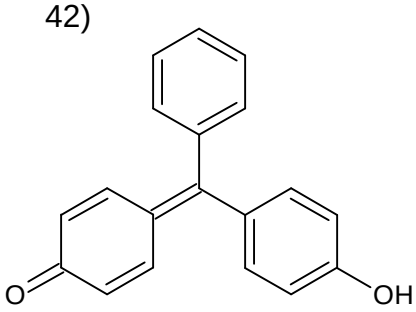


# CHAPTER 1

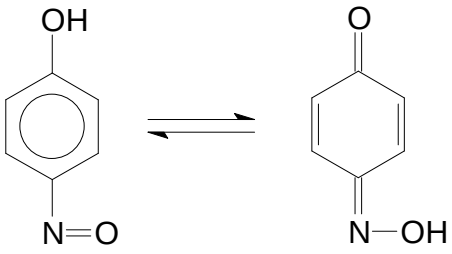
# INTRODUCTION

## 1.1 Statement of the research hypothesis

In previous work done in our laboratories,[1] a method was elaborated to produce phenolic mono-ethers in a simple one-pot process. In these procedures, when 4-hydroxyacetophenone and other 4-hydroxyketones were treated with ammonium peroxy-disulfate in an alcohol as reaction solvent and in the presence of concentrated sulphuric acid or other strong protonic acids, 4-alkoxyphenol resulted as the major product in good to excellent yield. To explain these observations, a reaction mechanism was proposed that involves the substitution of a hydroxyl-group (with elimination of water) by an alkoxy-group from an activated hydroquinone-benzoquinone complex (quinhydrone). In a slight variation of the above work,[1] it was also shown that 4-alkoxyphenol ethers can be produced in high yields (>90%) by generating small amounts of benzoquinone continuously from hydroquinone or substituted hydroquinones by means of electrochemical oxidation procedures.

Since this method of producing 4-alkoxyphenol ethers provides a very convenient way to modify hydroquinone and substituted hydroquinones to produce a variety of phenol mono-ethers, it was of interest to study the general scope of this reaction, including a more detailed investigation of the reaction mechanism at work, as well as the type of substrates that can be used as nucleophiles for substituting the *para*-hydroxyl group. In addition, it was also of interest to investigate whether other compounds that are also capable of forming the cyclohexa-2,5-diene structure, will interact in a manner analogous to the hydroquinone/benzoquinone couple. Two specific compounds were selected for this purpose, namely 4-nitrosophenol **1** and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one **3**. In the case of 4-nitrosophenol, an equilibrium exists in solution between the free phenol and 4-(hydroxyimino)

cyclohexa-2,5-dien-1-one **2** (Eqn. 1), while in the case of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one, there is an equilibrium between 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one **3** and the 4-(hydroxyphenyl) diphenylmethanol **4** (Eqn. 2).

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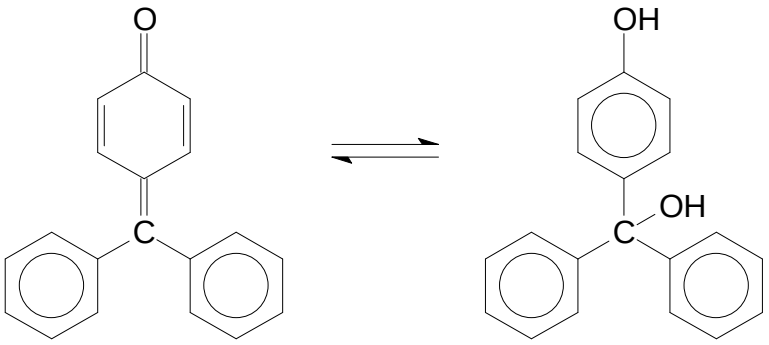



**3** **4** (2)

Thus, interaction of either the phenol form with benzoquinone, or the cyclohexa-2,5-diene form with hydroquinone in these two cases could lead to activation which should allow reaction with alcohols in the presence of either hydroquinone or benzoquinone in a manner analogous to the reaction of the hydroquinone/benzoquinone couple with alcohols in the presence of an acid catalyst.

## 1.2 General

The widespread commercial application of organic chemistry is generally considered to have started in the late 1850's with the development of the synthetic

dyestuffs industry. During the following 30 to 40 years the preparation of synthetic dyestuffs and the intermediates required for their manufacture became a major industry, and a number of other organic chemical products became commercially important. By 1900, the organic chemical industries were well established.[2] During the twentieth century, the industrial application of chemistry developed rapidly, and since then, the practice and the products of the chemical sciences have an all-pervading effect on our lives.

Apart from several notable exceptions, the South African chemical industry[3] has remained static over the last ten years. Indeed, in many cases, it has lost critical manufacturing capacity and skills; it has failed to expand and diversify significantly into higher value-added products; it has missed the opportunity to take a share of the high growth markets of the nineties, including such areas as electronic chemicals, specialty surfactants, active pharmaceutical ingredients, food and flavor additives and adhesives. Notwithstanding a number of strategic processes whose objectives were to increase downstream value-addition and integration, it remains predominantly an upstream, commodity-based industry that has not managed to break through its endemic growth barriers of a small local market because of the high cost of capital, distance from low-cost raw materials and inadequate human resources.

In early 2002, the Department of Trade and Industry published a document entitled Accelerating Growth and Development: The Contribution of an Integrated Manufacturing Strategy,[4] the purpose of which was to ‘invigorate the production of goods and services and create the conditions necessary for the retention and growth of output and employment in other sectors of the economy’. The document identified a number of requirements for micro-economic reform in South Africa, including the promotion of competitiveness and the development of customized services. Furthermore, the chemical industry, in view of its potential for growth and development, was highlighted as worthy of increased attention and a number of specific objectives were defined. However, the Integrated Manufacturing Strategy (IMS)[5] will on its own not be able to achieve the desired outcomes of growth and

development, as indeed is acknowledged in the document. For instance, the outcomes will also require appropriate and effective human resource development and technology strategies. The latter aspect has been a specific focus of the National Advisory Council of Innovation (NACI),[6] which is concerned that South Africa's R&D capability is lagging significantly behind competitor developing countries, and that this lag will reduce the country's competitiveness in world markets. In order to redress this situation, to underpin the new IMS and to stimulate investment in key technology, NACI commissioned an Advanced Manufacturing and Logistics Strategy with the requirement that the recommendations provide some radical, highly innovative and lateral solutions to leverage South Africa's manufacturing industry. In this context, the Chemical Sector Task Team (CSTT) proposed several strategic interventions,[7] including:

- Development of a new industry based upon the extraction of minerals from coal ash and low-value slag.
- Extension of the South African Nuclear Energy Corporation's (NECSA) expertise in fluorine generation and use in order to generate a range of fluorinated organic chemical intermediates.
- Development of a new range of performance chemicals that will improve the recovery of minerals in the mining sector (such as polymers used in solvent extraction processes).
- Establishment of new technology platforms that will develop technologies to decrease economies of scale for chemical plants and hence enable smaller production facilities to compete against the mega plants.
- Support for existing development efforts in low-cost diagnostics, aroma chemicals production, and development of biodegradable and high performance polymers, bio-diesel and products from alpha-olefins.
- A major initiative to build South Africa's first generic pharmaceutical actives plant in order to meet future demand for antibiotics and/or anti-retrovirals.
- The implementation of a highly integrated strategy to fully develop South Africa's ability to add maximum value to its natural resources.

Towards the end of 2004, the Department of Science and Technology launched its "Research Centres of Excellence Program" including a Centre of Excellence in Catalytic Processing housed at the University of Cape Town. This Centre of Excellence, called "c*change" identified several major research programs with a view to support other initiatives such as the IMS referred to above. One of these programs, the Small Volume Chemicals Programme, specifically addresses these strategic interventions, and this particular project forms part of this overall Small Volume Chemicals Program which focuses on "the development of chemical and technological expertise for the synthesis and/or production of phenolic chemicals, particularly chemical starting materials, intermediates and products". This particular project is focused on this objective and deals with the conversion of simple phenolic compounds to higher-value derivatives by catalytic oxidation technologies e.g. phenols to hydroquinones/benzoquinones and alkylphenols to phenolic ketones or aldehydes, etc.

There is little doubt that the world-wide chemical industry today is facing major economic and environmental challenges. We as scientists have a responsibility towards the efficiency and profitability of the industry by developing sustainable processes and technologies which will have long-term economic and environmental viability. The chemical industry has been continuously driven by this need for better quality products and more effective and efficient production procedures.[8]

In the past, phenol was essentially a coal tar extraction product,[9] but due to an increasing demand, synthetic methods replaced extraction from natural resources. In addition to the efficient synthesis of phenolic starting materials, efficient, effective and selective reaction procedures are also required for the transformation of phenolic compounds into further derivatised products.

Phenolic ethers are important as intermediates in the preparation of a number of industrially important chemicals such as perfumes, fragrances and pharmaceuticals.[10-14] They are also important chemicals in their own right, being

used as antioxidants in various consumables.[15-17] 4-Methoxyphenol for example, is regarded as a high volume chemical in the USA, and has a production volume exceeding five hundred thousand kilograms per year.[18-19] Many other un-substituted and substituted phenolic ethers also have significant demand in the international market.

These types of compounds are normally prepared by treating hydroquinone with alkylating agents such as the di-alkyl sulphates, haloalkanes or alcohols. The main problem in these preparative methodologies is that a complex mixture of products is usually obtained, including un-alkylated, mono-alkylated and di-alkylated compounds.[20] This implies the requirement of non-trivial and expensive separation procedures in order to obtain the desired mono-alkylated product.[21-22]
More efficient reactions for these types of products would therefore be quite welcome.

### 1.3 Objectives of the study

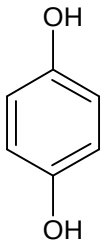
Many of the existing manufacturing routes to *para*-hydroxy-substituted phenolic mono-ethers involve complicated multi-step reactions, and some of them use alkylating agents that are extremely carcinogenic and thus render these reactions inherently unsafe. When dihydroxybenzene is alkylated to prepare these types of ethers, a complex separation of mono, di- and un-alkylated products is required at the end of reaction, this being a further limitation of these reactions.

The main purpose of this investigation was to study the selective substitution of one of the hydroxyl groups of hydroquinone, or other groups in similar substrates 4-nitrosophenol and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one), by alcohols and other reagents in the presence of benzoquinone and an acid catalyst so as to be able to evaluate the potential of this approach for the selective synthesis of 4-alkoxyphenols and similar compounds.

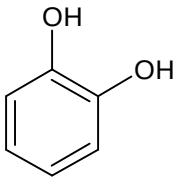
## 1.4 Overview of starting materials

### 1.4.1 Hydroquinone

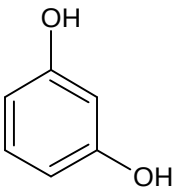
Hydroquinone, dihydroxybenzene, (chemical formula $C_6H_6O_2$) can exist in three different isomeric forms namely hydroquinone **5** [123-31-9] (or 1,4-dihydroxybenzene, p-dihydroxybenzene, 1,4-benzenediol, hydroquinol, quinol), catechol **6** [120-80-9] (or 1,2-dihydroxybenzene, 1,2-benzenediol, o-dihydroxybenzene) and resorcinol **7** [108-46-3] (or 1,3-dihydroxybenzene, 1,3-benzenediol).[23]




**5**




**6**




**7**

#### *1.4.1.1 Physical properties*

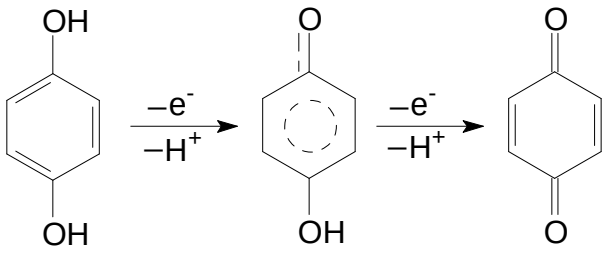
Hydroquinone is a colourless crystalline solid when pure. Three crystalline modifications exist: the stable α-form (mp = 173.8-174.8$^0$C) is obtained as hexagonal needles by crystallization from water; the labile γ-form (mp = 169$^0$C) is obtained as monoclinic prisms by sublimation; and the labile β-modification is obtained as needles or prisms by crystallization from methanol or isopropyl alcohol. Commercial grades of hydroquinone are typically white to off-white crystalline materials.[23]

#### *1.4.1.2 Chemical properties*

Hydroquinone is easily converted to p-benzoquinone by most oxidizing agents; even neutral aqueous solutions of hydroquinone darken on exposure to air. The rate of oxidation of hydroquinone by air is accelerated in alkaline solution. The

oxidation product can add water to give 1,2,4-benzenetriol. Further oxidation may result in the formation of humic acids.

Oxidation of hydroquinone involves loss of an electron and elimination of a proton to give the relatively stable semi-benzoquinone radical **8**. The ability of hydroquinone to act as an antioxidant is a consequence of the formation and stability of this radical. A second one-electron transfer and proton elimination results in the formation of p-benzoquinone **9**.

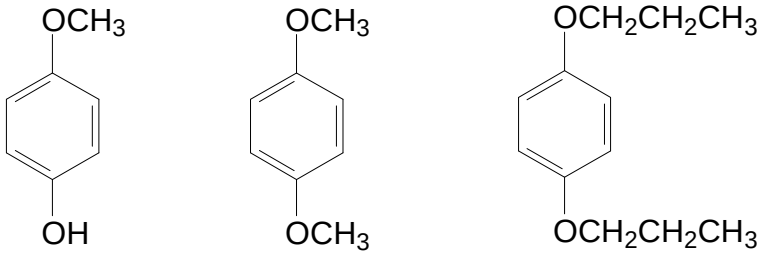



**5** **8** **9**

Hydroquinone and p-benzoquinone form the equimolar charge-transfer complex called quinhydrone. The quinhydrone complex is typically dark greenish-black, mp $171^0$C.

Hydroquinone is a reducing agent, whose reduction potential is sufficient to reduce silver halides. Because of this property, hydroquinone is widely used as a developing agent in photography.

The reactivity of hydroquinone is generally similar to phenol. One or both hydroxyl groups may be converted to an ether or ester. Commercially important oxygen derivatives include hydroquinone mono-methyl ether **10** [150-76-5], hydroquinone di-methyl ether **11** [150-78-7], and hydroquinone bis(2-hydroxyethyl)ether **12** [104-38-1].




**10** **11** **12**

Hydroquinone esters undergo the Fries rearrangement to give acyl-substituted hydroquinones. Hydroquinone reacts with alkylamines or arylamines to form substituted arylamines.[23]

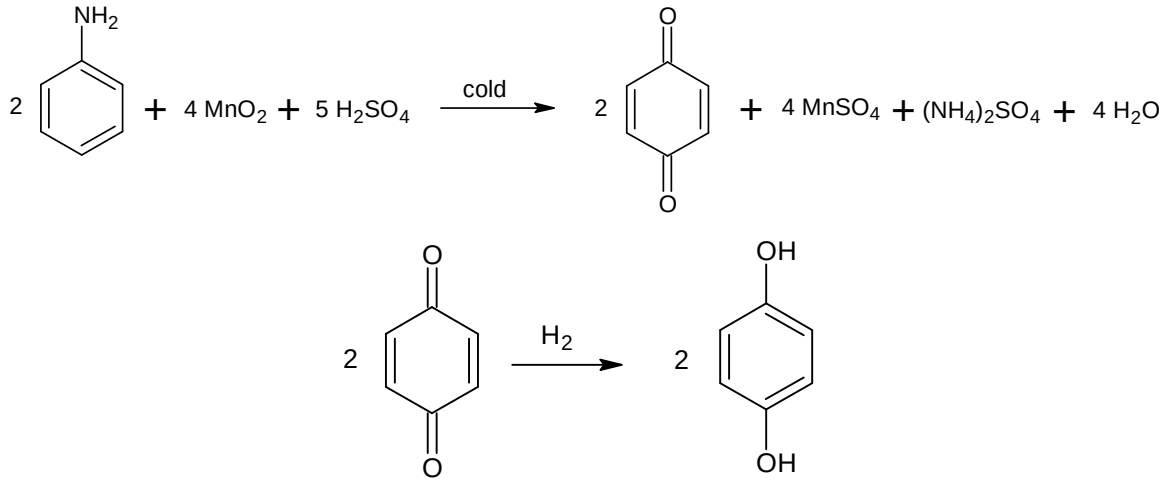
### *1.4.1.3 Production of hydroquinone*

Hydroquinone is prepared industrially using three major processes, namely by oxidation of aniline (Scheme 1), oxidation of p-di-isopropylbenzene (Scheme 2) and hydroxylation of phenol (Scheme 3).

**(i) Oxidation of aniline**.[15]

This is essentially a three-step process comprising:

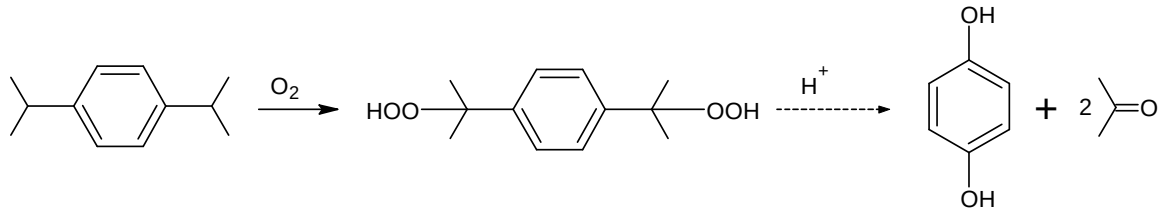
- An oxidation step in which aniline is oxidized with manganese dioxide (20% excess) in sulphuric acid at 5$^{o}$C to produce a mixture of benzoquinone, ammonium sulphate, and manganese sulphate.
- A separation step in which the benzoquinone is separated from the reaction mixture by steam stripping.
- A reduction step in which the benzoquinone is reduced to hydroquinone using either an iron suspension (55 – 65$^{o}$C), or by means of catalytic hydrogenation.




**Scheme-1: Oxidation of aniline**

**(ii) Selective oxidation of *m*- and *p*-di-isopropylbenzene.**[24]

This route involves the alkylation of benzene with propene over a solid acid catalyst to produce a mixture of *o*-, *m*-, and *p*-di-isopropylbenzenes. The *o*-di-isopropylbenzene is first isomerised to *p*- and *m*-di-isopropylbenzene before the mixture is oxidized to form a mixture of the respective hydroperoxides. This oxidation is usually carried out under slightly alkaline conditions in the absence of an autoxidation catalyst. Following concentration of the hydroperoxide mixture, acid cleavage (Hock rearrangement with a 0.2 – 1.0 % sulphuric acid solution at 60-80$^0$C) produces a mixture of hydroquinone and resorcinol, which are separated by distillation.

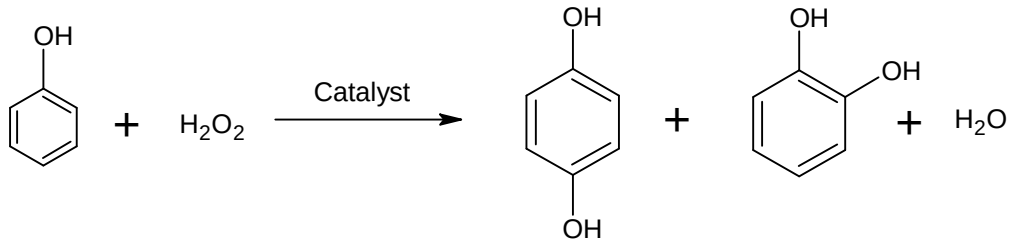



**Scheme-2: Oxidation of *p*-di-isopropylbenzene**

**(iii) Phenol hydroxylation**.[25]

A mixture of catechol and hydroquinone is obtained by hydroxylation of phenol with hydrogen peroxide in the presence of a catalyst. The ratio of catechol to hydroquinone ranges from about 3:1 to about 0.1:1 depending upon the nature of

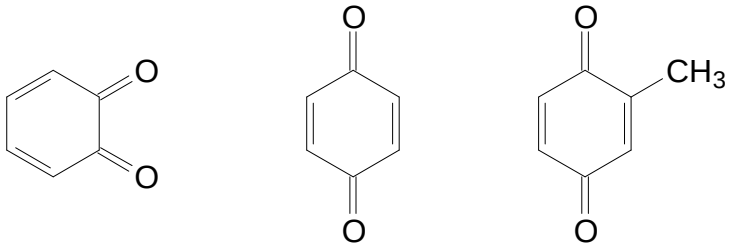
the catalyst and reaction conditions used. For certain shape-selective zeolite catalysts, selectivities to hydroquinone of up to 99% have been claimed.[26]




**Scheme-3: Hydroxylation of phenol**

### 1.4.2 Benzoquinone

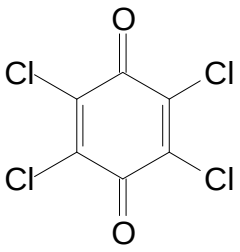
Benzoquinone (chemical formula $C_6H_4O_2$) plays significant and varied roles in metabolic processes and in synthetic reactions.[27-30] Benzoquinone exists in two isomeric modifications namely 1,2-benzoquinone **13** [583-63-1] and 1,4-benzoquinone **9** [106-51-4]. Both of these structures can be substituted with a wide variety of alkyl, aryl, halo, oxygen, nitrogen and sulphur groups.



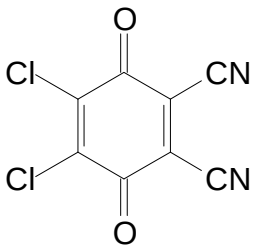

**13** **9** **14**

The quinones are most often named as derivatives of **13** or **9**, e.g., 2-methyl-1,4-benzoquinone **14** [553-97-9]. The CAS nomenclature of the quinones, e.g., 2,5-cyclohexadiene-1,4-dione for **9** is seldom used. As example, two important oxidizing agents, p-chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) **15** [118-75-2]

and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) **16** [84-58-2], are widely referred to by their trivial names.[31]




**15**




**16**

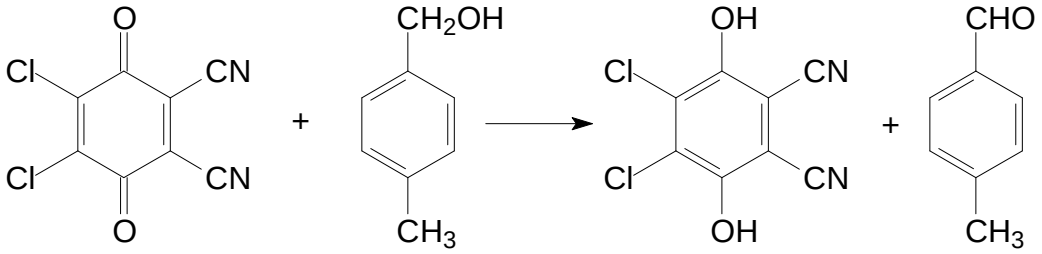
### *1.4.2.1 Physical Properties*

1,4-Benzoquinone (mp = $113^0$C) is soluble in most oxygenated organic solvents (viz, ether, alcohol etc.), and slightly soluble in petroleum ether, and insoluble in water. Crystallization from alcohol or sublimation produces yellow monoclinic prisms. The lower molecular mass benzoquinones have high-vapour pressures and pungent, irritating odors.[31]

### *1.4.2.2 Chemical Properties*

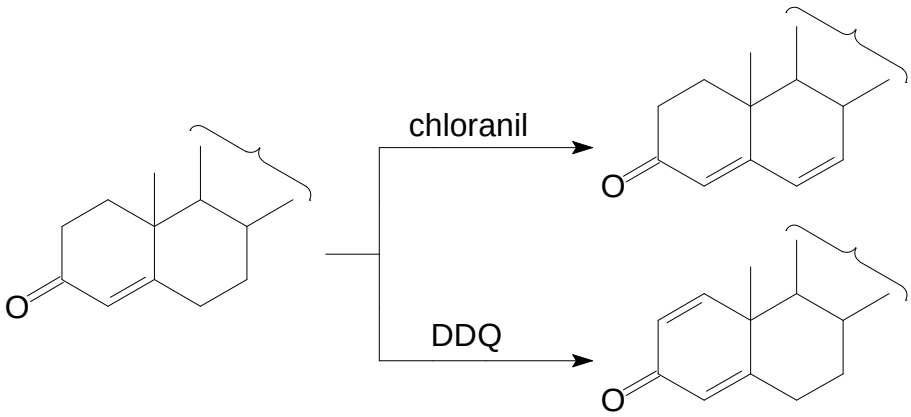
The quinones are important oxidants in synthetic and metabolic processes. The presence of an extensive array of conjugated double bond systems, especially the α,β-unsaturated ketone arrangement, increases the importance of quinones and allows the quinones to participate in a variety of reactions (Scheme 4). The acid-catalyzed Michael addition reaction is characteristic of these reactions, but Diels-Alder, electrophilic, and radical additions, as well as substitutions, are well documented.[32] There is also a growing literature related to the role of quinones in photochemical processes.[33] In efforts to understand the question of valence in organic molecules, A. Michael carried out one of the earliest quinone addition reactions.[34]

Quinones with high-oxidation potentials have significant practical importance and are often used in conversions involving delicate oxidations. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is often chosen as the oxidizing reagent because of its favourable combination of high-oxidation potential (ca. 1000mV) and great stability.[35]



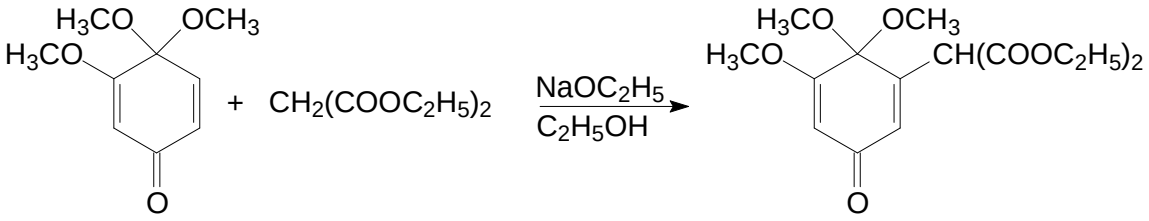

**Scheme-4: Preparation of p-tolualdehyde**

Chloranil **15** often finds application in the selective dehydrogenation (Scheme 5) of steroid ketones:[36]




**Scheme-5: Dehydrogenation of steroid ketones**

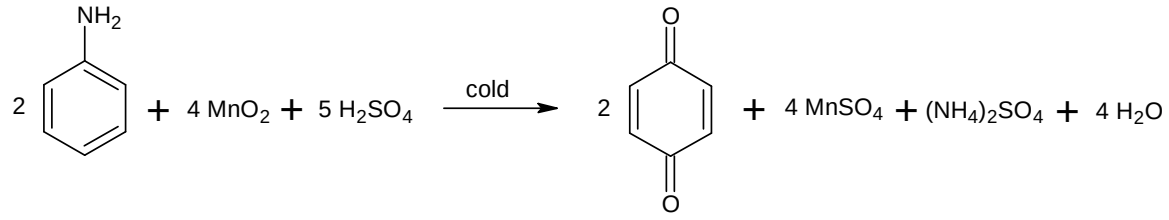
The useful change in product structure with DDQ **16** has been studied in detail.[37] The quinone monoacetals, e.g., 3,4,4-trimethoxycyclohexa-2,5-dien-1-one [64701-03-7], are useful in reactions requiring bases (Scheme 6), to which the quinones are especially sensitive.[38]




**Scheme-6: Preparation of quinone monoacetal ester (Michael addition)**

### *1.4.2.3 Production of 1,4-Benzoquinone*

With the exception of 1,4-benzoquinone, the simple quinones do not have a substantial market. There are various synthetic routes to 1,4-benzoquinone, but industrial scale preparation is still carried out by the oxidation of aniline (Scheme 7) or phenol in the presence of sulphuric acid and manganese dioxide (15-20% excess). The product is steam distilled, chilled and obtained in high yield and purity.




**Scheme-7: Oxidation of aniline**

### 1.4.3 Demand and consumption of hydroquinone and its derivatives

Consumption (in tons) of hydroquinone and its derivatives by geographical area is shown in Table 1.1, while demand for the hydroquinone and its derivatives are shown in Table 1.2, according to market segment. [39]

**Table 1.1: Consumption of hydroquinone and derivatives (1987)**

| | |
|---|---|
| United States | 13100 |
| Europe | 9600 |
| Japan | 3800 |
| Other | 4800 |
| Total | 31300 |

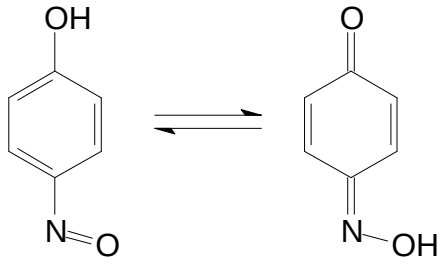
**Table 1.2: Worldwide demand for hydroquinone and its derivatives by market segment (1987)**

| Market segment | Demand | |
|---|---|---|
| | Tonne | % of total |
| Photography | 11600 | 37 |
| Rubber industry | 8100 | 26 |
| Monomer inhibitors | 3100 | 10 |
| Dyes and pigments | 2800 | 9 |
| Antioxidants | 650 | 2 |
| Agricultural chemicals | 650 | 2 |
| Others | 4400 | 14 |
| Total | 31300 | 100 |

### 1.4.4 4-Nitrosophenol

4-Nitrosophenol (chemical formula $C_6H_5NO_2$) is a substituted phenol containing the nitroso (-N=O) group at position *para*- to the hydroxyl group. Nitroso groups and azo (-N=N-) groups impart colour to aromatic compounds as these groups absorb light in the visible wavelength range. Nitroso groups are strongly electron withdrawing and represent C=O rather than the nitro group. The polarization of the N=O bond is responsible for imparting characteristics representing C=O groups. Nitroso compounds tend to dimerise. They also undergo addition of nucleophiles and condense with primary amines and the anions of active methylene

compounds. Nitroso groups are useful in addition and condensation reactions, stable nitroxide radical preparations, and isomerization to oximes. Nitroso compounds are also useful intermediates for the synthesis of target materials like sulphur-containing vat dyes and sulfide dyes. 4-Nitrosophenol **1** exists in equilibrium with 4-(hydroxyimino)cyclohexa-2,5-dien-1-one **2** in solution.[40]



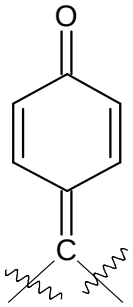

**1** **2**

### *1.4.4.1 Physical properties*

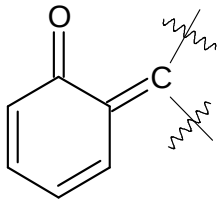
4-Nitrosophenol is a black coloured solid [mp = ca.132 - 144$^0$C (decomposes)] that is soluble in most oxygenated organic solvents (ether, alcohol), and insoluble in water. When sublimated it produces pale yellow crystals. It can ignite spontaneously on storage if impure. It has a pungent, irritating odour.[40,41]

## 1.4.5 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one

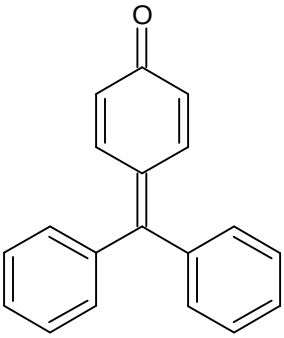
4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one is a compound containing 4-methylenecyclohexa-2,5-dien-1-one **17**, or 2-methylenecyclohexa-3,5-dien-1-one **18** fragment. 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one itself referred specifically by its trivial name such as fuchsone **3**. 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one **3** occurs in equilibrium in aqueous solution with the hydrated form 4-(hydroxyphenyl)diphenylmethanol **4**. 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one is a useful intermediate for the synthesis of materials like p-dihydroxylated aromatic compounds via oxidation reactions.[42]




**17**




**18**




**3**

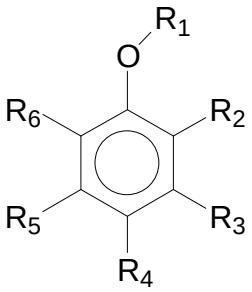
### *1.4.5.1 Physical properties*

4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one is a yellow-orange coloured solid when pure, having a molecular mass of 258, mp 166-169$^0$C, and is soluble in most oxygenated organic solvents (ether, alcohol), and insoluble in water. When sublimated it produces pale yellow crystals.[12]

## 1.5 Overview of phenolic ethers

### 1.5.1 Phenolic ethers

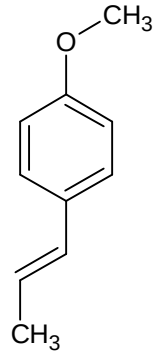
Phenolic ethers have the general formula **19**:



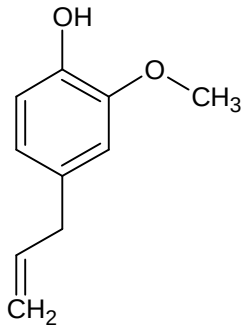

**19**

The phenyl ring may either be unsubstituted (or $R_2$ - $R_6$ = H), or mono- or poly-substituted. Furthermore, $R_1$ may be a substituted or unsubstituted aliphatic or aromatic hydrocarbon.

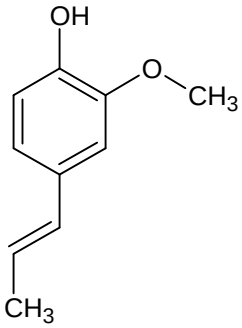
Phenolic ethers can be isolated from natural sources such as volatile oils, e.g. the anise fragrance anethole **20,** the clove fragrances eugenole **21** and isoeugenole **22**.[43]




**20**



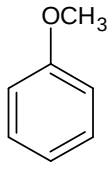

**21**



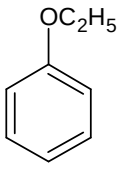

**22**

### 1.5.2 Physical properties of phenolic ethers

Most phenolic ethers have a pleasant, characteristic smell. The lighter phenolic ethers are colourless liquids that are insoluble in water, soluble in organic solvents, and stable to alkalis. Some representative phenolic ethers with their boiling points and molecular formulas are phenyl methyl ether **23** {anisole; bp (101.3 kPa) $155^0$C $[C_7H_8O]$}, phenyl ethyl ether **24** {phenetole; bp (101.3 kPa) $170^0$C $[C_8H_{10}O]$}, diphenyl ether **25** {bp (101.3 kPa) $257.9^0$C $[C_{12}H_{10}O]$}, veratrole **26** {bp (101.3 kPa) $206^0$C $[C_8H_{10}O_2]$}, 1,3-benzodioxole **27** {bp (101.3 kPa) $172^0$C $[C_7H_6O_2]$} and 4-methoxyphenol **10** {bp (101.3 kPa) $243^0$C $[C_7H_8O_2]$}.[44]




**23**

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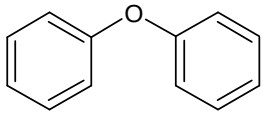


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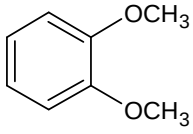


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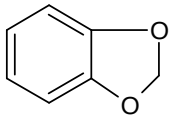
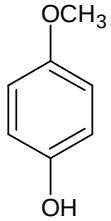



**27**




**10**

### 1.5.3 Chemical properties of phenolic ethers

The ether linkage in phenolic ethers is very stable. The carbon-oxygen bond in completely aromatic phenolic ethers such as diphenyl ether is cleaved only under drastic conditions, e.g. with alkalis at high temperature and pressure; in contrast, the aliphatic carbon-oxygen bond in anisole, for example, is split by treatment with strong acids such as hydrogen iodide to form phenol and an alkyl iodide. Sterically hindered methoxy groups can be cleaved selectively with $BCl_3$.

The phenyl ring is susceptible to substitution reactions, including hydroxylation, nitration, halogenation, and sulfonation. Phenol ethers can be alkylated or acylated by Friedel-Crafts reactions. Aromatic–aliphatic ethers, however, can also be cleaved in the presence of Friedel-Crafts catalysts at high temperatures.[44]

### 1.5.4 Uses and demand of phenolic ethers

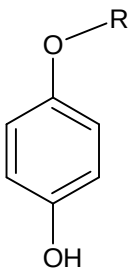
Phenolic ethers are primarily used as intermediates in the production of a variety of chemical products such as polymerization inhibitors, storage stabilizers for photosensitive materials, ink corrosion inhibitors, antioxidants, fibre swelling agents, perfumes, dyes, flavours and fragrances, agrochemicals and pharmaceuticals.[10-14] One of the most important uses of phenolic ethers is as antioxidants.[15-17]

In order to facilitate the discussion on the other major uses of some of the economically important phenolic ethers, these compounds have been classified according to the functional group present on the benzene ring, namely:

1. Glycosides of hydroquinone
2. Alkoxy-substituted alkylphenol
3. Alkoxy-substituted phenols
4. Trialkoxybenzenes
5. Miscellaneous

### *1.5.4.1 Glycosides of hydroquinone*

The glycosides of hydroquinone can be represented as the following general formula **28**:

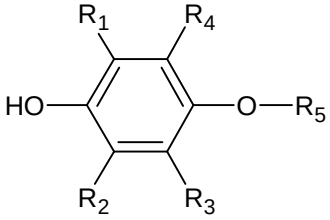



**28**

In the above, R may represent a pentose residue, a hexose residue, an amino sugar residue or an uronic acid residue. These compounds are useful ingredients in skin treatment compositions that comprise at least one glycoside of hydroquinone and one or more UV absorbers. The glycosides **28** are essentially used for their skin depigmentation effects whilst also effectively suppressing skin irritation caused by the UV absorber.[45]

### *1.5.4.2 Alkoxy-substituted alkylphenols*

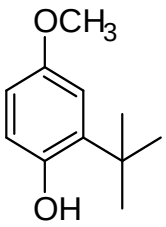
This group of compounds with the general chemical structure **29** has significant industrial importance.



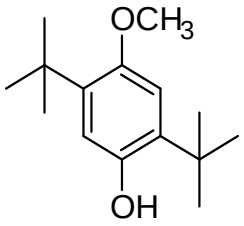

**29**

In the above structure, $R_1$ to $R_4$ may be a hydrogen atom, a linear alkyl group, or a branched alkyl group. Examples of commercially important compounds of this

group include 2-(*tert*-butyl)-4-methoxyphenol **30** and 2,5-bis(*tert*-butyl)-4-methoxyphenol **31**. Food, feeds and cosmetics commonly contain antioxidants to prevent colour fading or discoloration, a change in aroma and formation of peroxides during preservation.[46] 2-(*tert*-Butyl)-4-methoxyphenol **30**, or more commonly known as butylated hydroxyanisole (BHA), is an excellent example of an antioxidant used in such applications.[39]




**30**

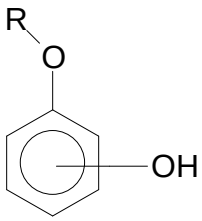



**31**

2,5-Bis(*tert*-butyl)-4-methoxyphenol **31** is a useful compound as an intermediate in the production of industrial chemicals, agrochemicals, dyes, medicines and also as a raw material for antioxidants and stabilizers. It is most commonly produced by reacting 4-methoxyphenol with isobutylene in the presence of methanesulfonic acid as an acid catalyst.[11]

### *1.5.4.3 Alkoxy-substituted phenols*

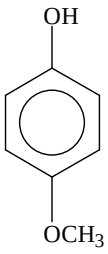
Phenolic ethers of this group have the following general formula **32**:



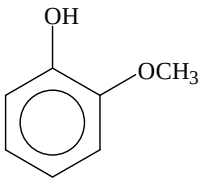

**32**

In the above structure, R is an alkyl group (e.g. methyl, ethyl, propyl, etc.).

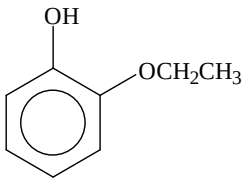
The phenolic ether 4-methoxyphenol **10** is used extensively (together with hydroquinone and benzoquinone) in the rubber industry and as polymerization inhibitors in the vinyl monomer industry. It is, for example, used as a polymerization inhibitor for acrylic or methacrylic acid derivatives.[47] Other uses include as a storage stabilizer for photosensitive materials, antioxidants, ink corrosion inhibitors, acrylamide gel collapse preventives, fibre-swelling agents, synthetic intermediate for agrochemicals, pharmaceuticals, dyes, and skin depigmentation agents.[10,44]



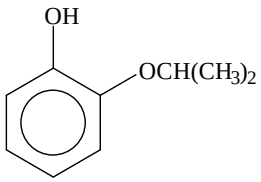

**10**




**33**




**34**




**35**

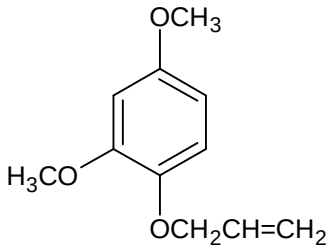
2-Methoxyphenol (guaiacol) **33** is present in many essential oils and is used as a flavour compound in many foods.[44] It is also used as an antioxidant for fats, oils, and vitamins, and as a polymerization inhibitor.[44] Guaiacol is also used extensively as a synthetic intermediate in the pharmaceutical, flavour and fragrance industries (e.g. for the synthesis of vanillin). Furthermore, it is used in the synthesis of veratrole, an intermediate in the synthesis of alkaloids and pharmaceuticals.[47] The therapeutical use of 2-methoxyphenol is both external, as an antiseptic, anaesthetic and as rheumatoid rub-ins, and introspective, as an expectorant.[44]

2-Ethoxyphenol **34** is used as an intermediate in the synthesis of ethyl vanillin, used in place of vanillin in specialty confectionary.[44]

2-Isopropoxyphenol **35** is use as a starting material for the synthesis of the pesticide Propoxur (2-isopropoxyphenyl methylcarbamate).[47]

### *1.5.4.4 Trialkoxybenzene*

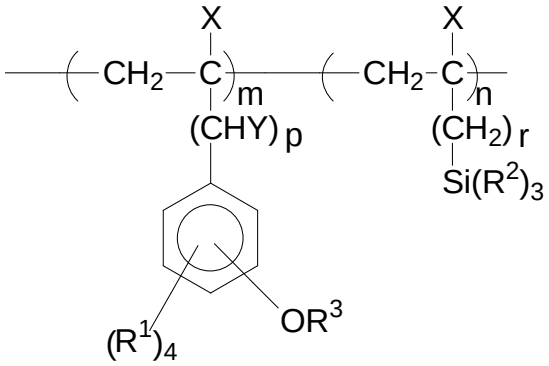
The phenolic ethers of this group find application as intermediates in the synthesis of isochromanquinones, which possess biological activity. 1-Allyloxy-2,4-dimethoxybenzene **36,** for example, has medicinal value and may be used to inhibit the growth of fungi, gram-positive pathogens and mycoplasma.[48]




**36**

### *1.5.4.5 Miscellaneous*

The copolymers of alkenylsilanes **37** with either alkenylphenol or alkenylphenol ethers are suitable for use as base polymers for dry-etch resistant, high resolution resists for UV-, deep UV-, electron-, and roentgen-rays. These copolymers are also useful positive photoresistants.[49] These compounds have the following general formula:




**37**

where, m + n = 1, p and r denote each 0, 1 or 2 (and that independently of each other),

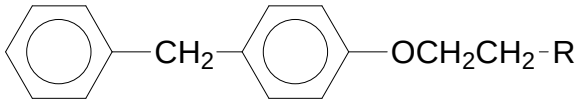
X = H, $CH_3$, $C_2H_5$ or halogens (i.e. F, Cl, Br, or I),

Y= H, $CH_3$ or halogen,

$R^1$ = H, halogen, alkyl (i.e. $CH_3$ and $C_2H_5$) or halogen alkyl,

$R^2$ = H, $CH_3$, $C_2H_5$, $C_3H_7$, or $C_6H_5$ and
$R^3$ = H or $R^1$

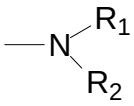
Certain amino-alkyl phenol ethers **38** have potential utility in the treatment of cancer as they have been shown to be cytotoxic to human breast cancer cells. One of the most widely used of these compounds is 1-(p-β-dimethylaminoethoxyphenyl)-trans-1,2-diphenylbut-1-ene (tamoxifen).[50] This group of compounds also has pronounced anti-histamine effects.[51]



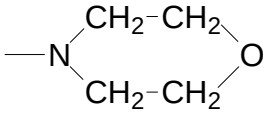
**38**

where R is either

(i)

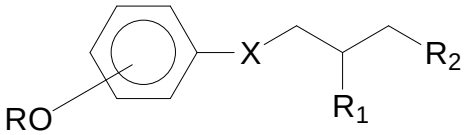


(ii)



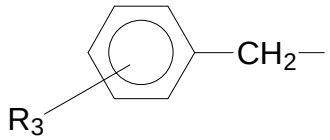
and $R_1$ and $R_2$ are a methyl or ethyl group.

Some alkyl or benzyl phenol ethers **39** exhibit an inhibitive action on monoamine oxydase in general and particularly on β-monoamine oxydase. These have potential therapeutic uses including the treatment of neurological disorders.[52]



**39**

where R represents a $C_3$-$C_6$ alkyl group or a benzyl group with the formula:

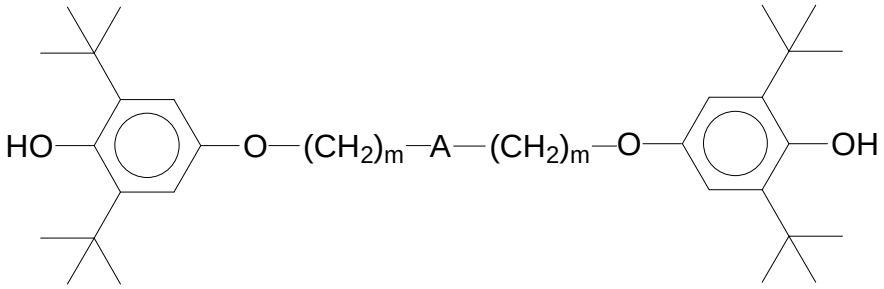



in which:

$R_3$ = H, a halogen, a $C_1$-$C_4$ alkyl, a $C_1$-$C_4$ alkoxy group, $CF_3$, $NO_2$ or a CN group, X = O or $–CH_2$, and

$R_1$ and $R_2$ represents a $C_1$-$C_4$ alkoxy or alkyl group or –OH.

A special group of phenol ethers having the general structure **40** are effective medicines for early atheromatosis and progressive arteriosclerosis.[53]




**40**

In the above structure, m represents a number between 1 and 6, and A is a bond, a methylene group, a keto group or a –CH(OH)- group.

## 1.6 Preparation methods of phenolic ethers

Because of their significant demand in international markets, the production of phenolic ethers is governed essentially by market forces. The dihydroxyphenols, hydroquinone and catechol, are the most important starting materials for the preparation of alkoxyphenols.[10,13,14,16,17,20,21,54]

Many phenols are formed during the processing of the more complex carbon compounds, especially of wood and coal-tars, from which they may be isolated by extraction with a base such as sodium hydroxide solution, in which they dissolve.[55] Phenols and substituted phenols from such sources or from synthetically produced

sources can be converted into dihydroxybenzenes (hydroquinone, catechol) by oxidation.[56]

Although phenolic ethers can be prepared by the reaction of dihydroxyphenols or substituted dihydroxyphenols with alkyl or aryl halides, or by reaction of phenol and substituted phenols with sodium alkoxide reagents, these procedures are never straightforward. Thus, hydroquinone mono ethers are generally difficult to prepare in high purity due to the complex separation of the mono-, di- and un-alkylated dihydroxybenzene. To minimize this problem, low conversions are usually required which have a significant impact on the manufacturing cost.[22] Some of the more important preparation methods of phenolic ethers are briefly discussed below.

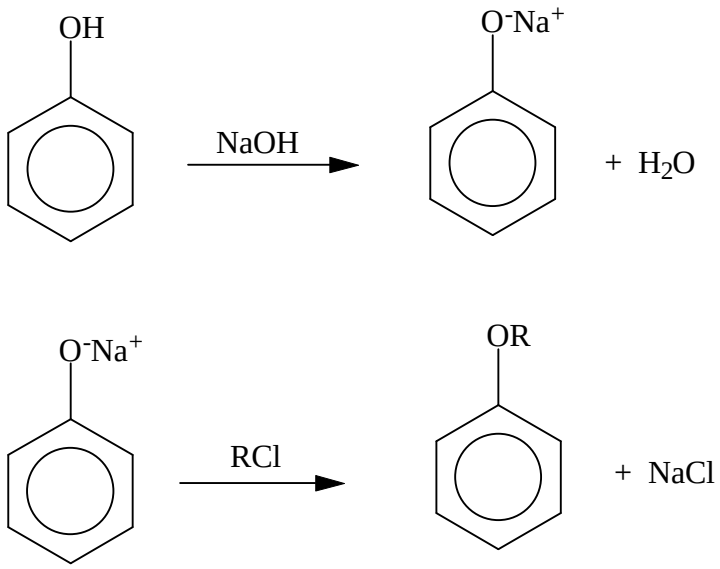
### 1.6.1 Preparation of phenolic ethers and hydroxy-substituted phenol ethers from phenols and dihydroxybenzenes

There are essentially two approaches to the preparation of alkoxy- or aryloxy-substituted phenols from phenols (or substituted phenols) and dihydroxybenzenes (or substituted dihydroxybenzenes), namely:

- Etherification of phenols using alkyl halides or sulphates as alkylating/arylating agents; and
- Etherification of phenol using alcohols.

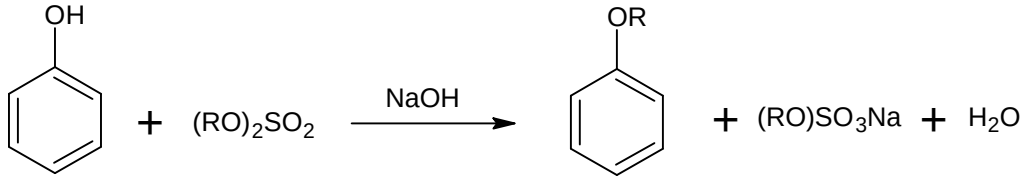
#### *1.6.1.1 Etherification of phenols using alkyl halides or sulphates as alkylating/arylating agents*

Nearly all phenol ethers can be prepared by the reaction of phenol with alkyl or arylhalides (preferably chlorides) in weakly basic aqueous media. This well known method for the preparation of ethers is generally known as the Williamson ether synthesis (Scheme 8). The phenoxide ion, which is formed first by reacting the phenol with alkali, serves as nucleophile.[44]




**Scheme-8: Williamson ether synthesis**

The short-chain aliphatic group phenolic ethers are usually synthesized by using dialkyl sulphates as alkylating agents in basic medium (Scheme 9).[44]



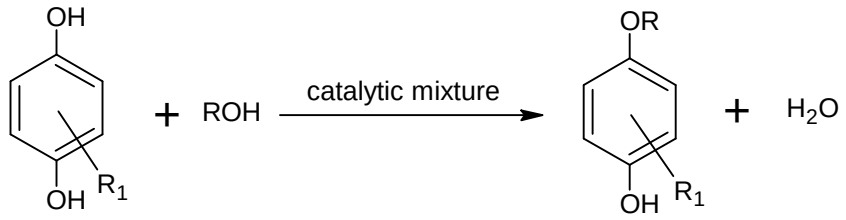

**Scheme-9: Etherification of phenols by dialkyl sulphates**

### *1.6.1.2 Etherification of phenols using alcohols*

The second method for the preparation of phenol ethers is the etherification of phenol or dihydroxybenzenes with aliphatic alcohols in the presence of a solid acid catalyst such as an ion exchange resin, or a silica-alumina catalyst. This reaction is normally carried out using excess phenol to suppress formation of dialkyl ether.[44]

4-Methoxyphenol, for example, may be obtained in high yields by reacting hydroquinone and methanol in the presence of a solid acid catalyst such as silica-alumina in a flow reactor at 200 - 350$^0$C under a pressure of 0.5-10Mpa. The molar

ratio of methanol to hydroquinone is in the order of 3:30, and the reagents are continuously fed to the reactor.[10] Hydroquinone mono ethers can also be prepared by reacting substituted/unsubstituted hydroquinone with alcohols in the presence of heteropoly acids such as heteropolymolybdic acid or heteropolytungstic acid (Scheme 10).[57]




where R represents an alkyl, alkoxy-alkyl, cycloalkyl, aryl-alkyl, or cycloalkyl-alkyl,
$R_1$ is hydrogen or alkyl, cycloalkyl, aryl-alkyl, or cycloalkyl-alkyl group

**Scheme-10: Etherification of phenols using alcohols**

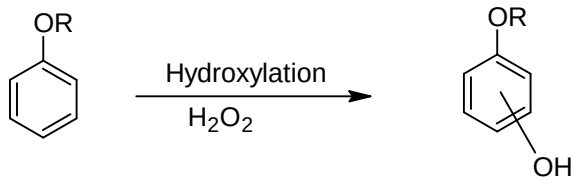
The synthesis of 4-methoxyphenol by the reaction of hydroquinone in the presence of 1,4-benzoquione with methanol and in the presence of sulphuric acid has also been reported.[20,21,58]

Mono ethers of hydroquinone can also be prepared by reacting the corresponding hydroquinones with the desired alcohol in the presence of a catalytic mixture consisting of a strong acid, a halogen or a hydrohalic acid selected from HBr, HI, $I_2$ and $Br_2$, and $H_2O_2$ in a molar amount lower than that of the starting hydroquinone.[54]

As in the case of hydroquinone, alkylation of catechol can be achieved similarly by reacting with alcohol in the presence of phosphoric acid or an ion exchange resin.[44]

### 1.6.2 Preparation of hydroxy-substituted phenol ethers from alkoxy- or aryloxybenzenes

Alkoxy or aryloxy-substituted phenols may also be prepared by hydroxylation of the corresponding alkoxy- or aryloxybenzene (Scheme 11) by reacting the phenol ether with hydrogen peroxide in the presence of a catalyst.[59,60]




where R represents an alkyl or aryl group

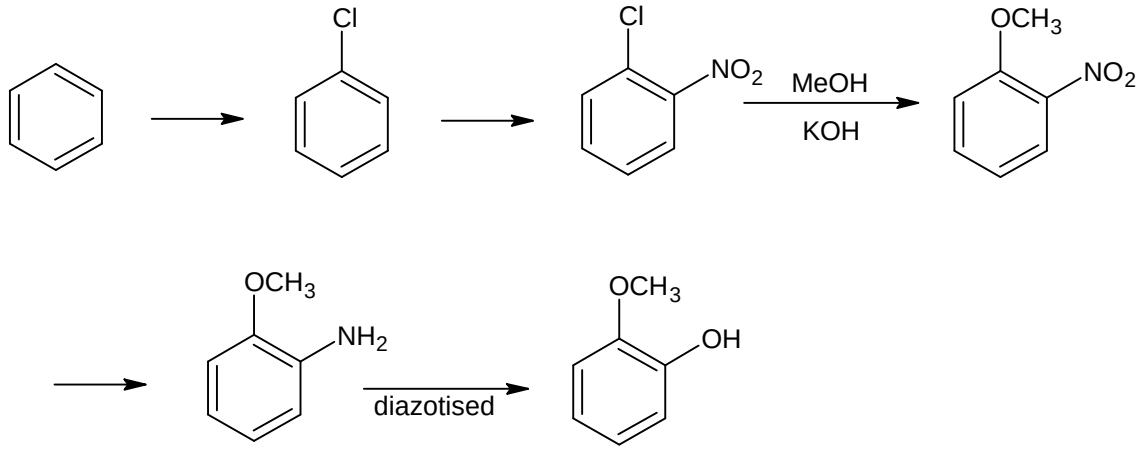
**Scheme-11: Hydroxylation of alkoxyphenol**

Several examples of this approach, which are essentially the same as for the hydroxylation of phenol to hydroquinone and catechol, may be found in the literature.[59-61] Thus, typical catalysts include the use of phosphoric acid in the presence of an alkali metal or alkaline earth metal salt. Another process for the preparation of alkoxyphenol ethers is the oxidation of phenol ethers with hydrogen peroxide in the presence of ketone or with a ketone peroxide at temperatures between $20^0$ and $250^0$C in the presence of a catalyst such as activated clay, boric acid or a boric acid derivative.[61]

The hydroxylation of phenol ethers is also possible by means of electrochemical oxidation. The electrolytic hydroxylation of anisole, for example, performed in the presence of feric(III)chloride as catalyst in an $O_2$ atmosphere produced a mixture of 2-methoxyphenol and 4-methoxyphenol.[62]

### 1.6.3 Preparation of hydroxy-substituted phenol ethers from halobenzenes

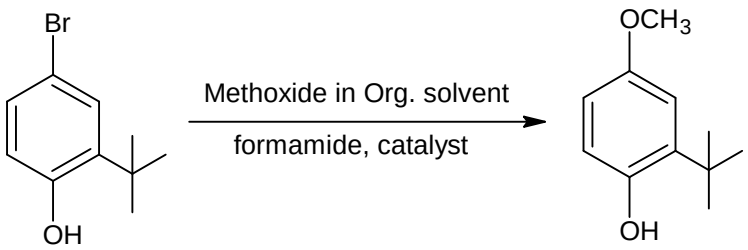
2-Alkoxyphenols such as 2-methoxyphenol can be prepared from benzene by the series of reactions depicted in Scheme 12.




**Scheme-12: Preparation of hydroxy-substituted phenol ethers from halobenzenes**

In this reaction, benzene is first converted into chlorobenzene, followed by nitration of chlorobenzene to obtain 1-chloro-2-nitrobenzene. This intermediate is then treated with a mixture of methanol and potassium hydroxide to obtain 1-methoxy-2-nitrobenzene, which is subsequently hydrogenated to give 1-amino-2-methoxybenzene. The desired product 2-methoxyphenol is obtained from 1-amino-2-methoxybenzene by diazotization.

In a different approach, 2-*tert*-butyl-4-methoxyphenol may be produced from 4-bromo-2-*tert*-butylphenol by reacting with sodium methoxide in an organic solvent (Scheme 13). This process affords only the desired 2-isomer and so avoids the need for a complex separation of different isomers produced by other methods.[63]

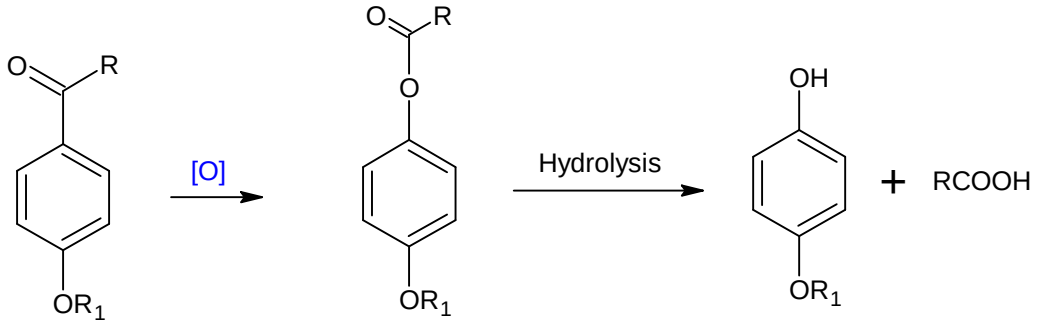



**Scheme-13: Preparation of tert-butyl alkoxy-substituted phenol**

For this reaction it is important that formamide and a catalyst of copper, cuprous bromide, bronze and potassium iodide, or of copper hydroxycarbonate and sodium sulphite are present.

### 1.6.4 Preparation of hydroxy-substituted phenol ethers from alkoxy or aryloxy-substituted aromatic aldehydes or ketones

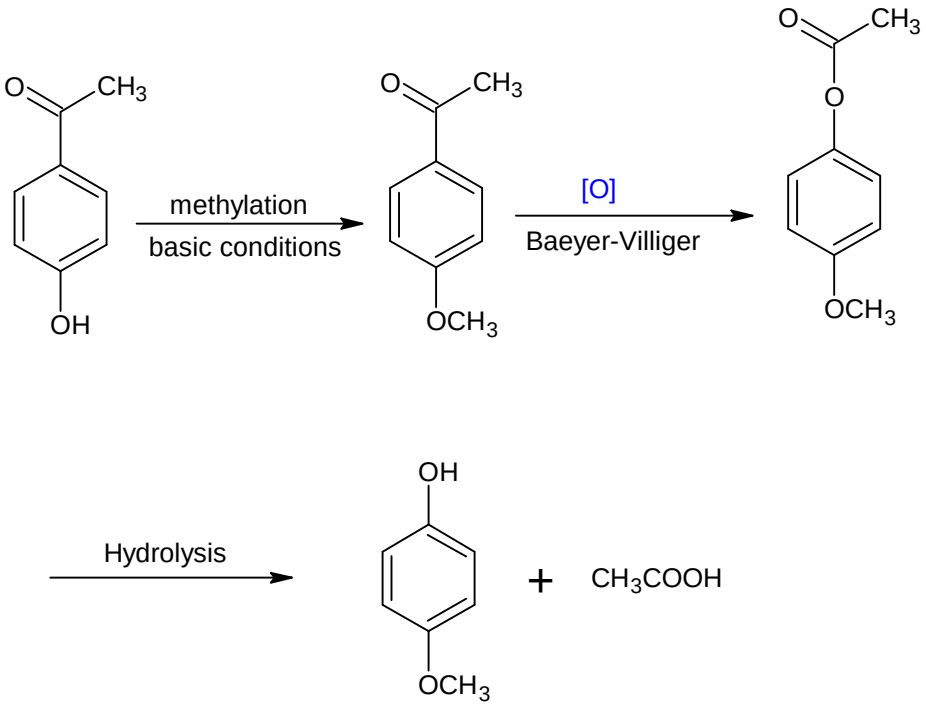
Hydroxy-substituted phenol ethers can be prepared very effectively by means of the well-known Baeyer-Villiger rearrangement reaction of alkoxy/aryloxy-substituted aldehydes or ketones.[64-66] During this rearrangement reaction, an oxygen atom is effectively inserted between the aryl and carbonyl groups by treatment of the aldehyde/ketone with a suitable oxidant to form a phenyl carboxylate. The resultant phenyl carboxylate may then be hydrolysed under acidic conditions either in situ or in a separate step, to the desired alkoxy/aryloxyphenol (Scheme 14). Different oxidizing agents may be used for the oxidation step, including peracids, hydrogen peroxide, and inorganic oxidants such as peroxydisulfate.[67]




**Scheme-14: Baeyer-Villiger rearrangement reaction**

### 1.6.5 Preparation of hydroxy-substituted phenol ethers from substituted or unsubstituted hydroxybenzaldehydes or hydroxyacetophenones

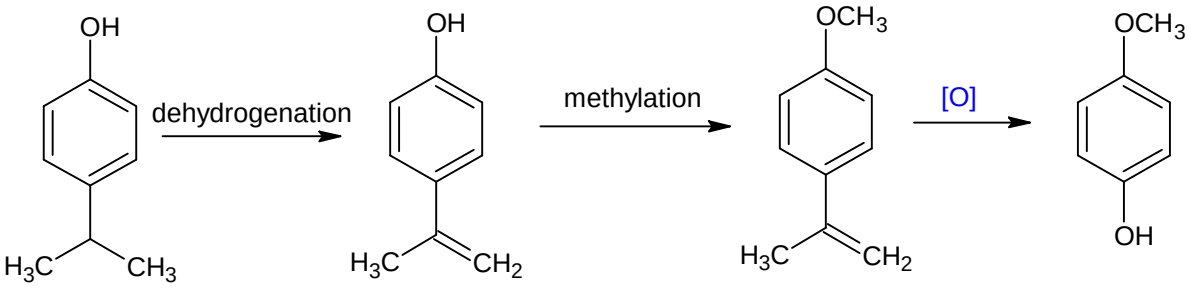
In a related reaction, hydroxy-substituted phenol ethers may be produced from the corresponding 4-hydroxybenzaldehydes or 4-hydroxyacetophenones by first alkylating the starting material and then performing a Baeyer-Villiger oxidation reaction in the normal manner (Scheme 15).[68]




**Scheme-15: Methylation followed by the Baeyer-Villiger oxidation reaction**

### 1.6.6 Preparation of hydroxy-substituted phenol ethers from alkylphenols

Hydroxyanisoles and alkylated hydroxyanisoles may be produced from alkylphenols by dehydrogenating *p*-isopropylphenol to first form *p*-isopropenylphenol, which is then reacted with a methylating agent to obtain *p*-isopropenylanisole. This intermediate is then oxidized with acidic hydrogen peroxide to obtain *p*-hydroxyanisole (Scheme 16).[69]



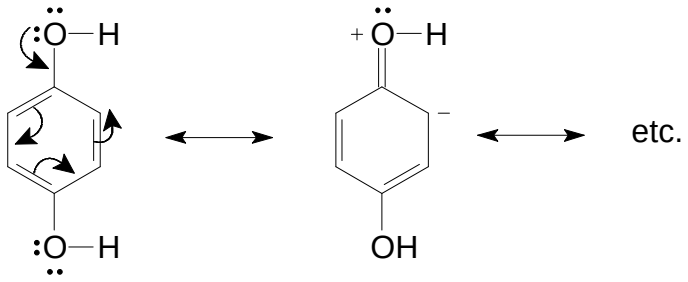

**Scheme-16: Preparation of hydroxy-substituted phenol ethers from alkylphenols**

## 1.7 Hydroquinone-Benzoquinone π-electron complex

The hydroquinone-benzoquinone π-electron complex can be obtained by mixing equivalent quantities of *p*-benzoquinone and hydroquinone, which is stable enough to be isolated and is known as a quinhydrone complex. Quinhydrone is a green crystalline solid, which is soluble in hot water. It is incompatible with strong oxidizing agents.[70] Quinhydrone consists of one molecule of each *p*-benzoquinone and hydroquinone and was once thought to be a molecular compound held together by hydrogen bonding between the two molecules. However, it became apparent that other compounds, which are incapable of undergoing hydrogen bonding, also form quinhydrone-type compounds. Thus, phenol, hydroquinone ethers or hexamethylbenzene can all take the place of hydroquinone.[71] In the presence of light, an electron is transferred from hydroquinone (donor) to *p*-benzoquinone (acceptor) giving quinhydrone, with characteristic purple color.[71]

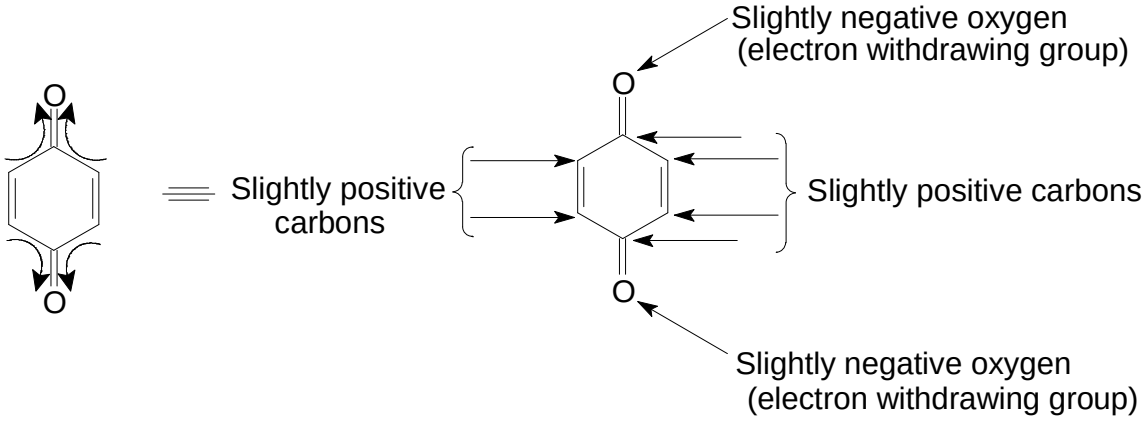
The formation of these types of adducts is the result of reciprocal interaction between the two π-electron systems. This takes place between two compounds because of mesomeric (+M) or inductive (-I) effects which cause the one compound to be π-electron-rich (an electron donor), whilst the other is π-electron-deficient (an electron acceptor). The p-benzoquinone:hydroquinone (1:1) adducts with this property are called "charge transfer complexes".[71]

In hydroquinone there is a positive mesomeric effect (+M) as a result of the lone pairs of electrons present on the oxygen atoms, which might be donated back into the ring through the π-electron system as shown in Scheme 17.




**Scheme-17: The positive mesomeric effect in hydroquinone**

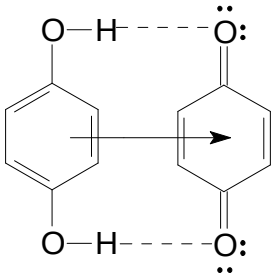
However, in the case of benzoquinone, the presence of the two carbonyl groups ensures that there is a negative inductive effect (-I) experienced in its ring. Since the carbonyl groups are strongly electron withdrawing, they cause all the carbon atoms of the ring to be slightly positive as illustrated in Scheme 18.




**Scheme-18: The negative inductive effect in benzoquinone**

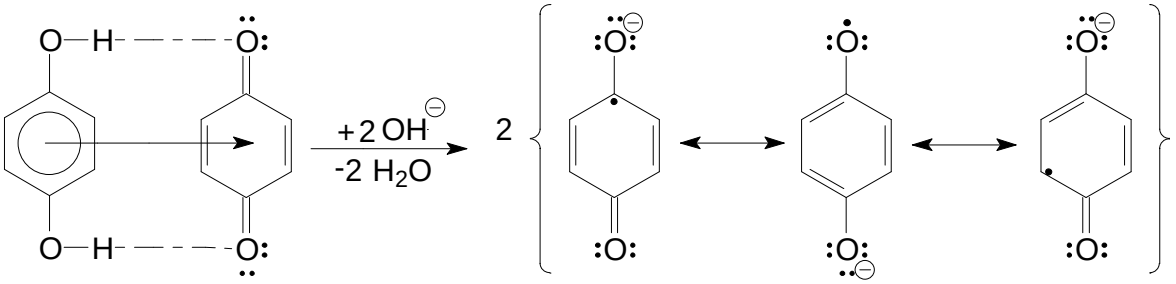
Consequently, in the case of hydroquinone and benzoquinone, the electron density is more on the hydroquinone ring as compared to the electron density on the benzoquinone ring because of the lone pair of electron donation of the OH group of hydroquinone to the aromatic ring. This difference in electron density between these ring systems is apparently the driving force for complex formation between

the two molecules in which hydroquinone behaves as an electron donor, donating electrons to the benzoquinone π-electron system. The benzoquinone therefore acts as an electron acceptor, accepting electrons from the hydroquinone π-electron system. The charge-transfer complex formed between these two molecules is further stabilized by two hydrogen bonds. The chemical structure for this complex, which is commercially available in this form (quinhydrone) can be represented as shown in Scheme 19.



**Scheme-19: Quinhydrone charge-transfer complex**

In alkaline media, quinhydrones are unstable and they dissociate with one electron from the donor being transferred to the acceptor to produce semiquinone anions. These radical anions are stabilized by mesomerism (Scheme 20). The unpaired electron is delocalized over all the carbon atoms and the oxygen atoms.[71]




**Scheme-20: Dissociation of quinhydrone**

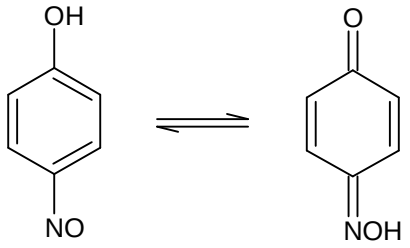
## 1.8 Hydrogen-bonding ability of phenol and its derivatives

For many years, phenols have been well recognized as participants in hydrogen bonding. At the first international conference (1957) on hydrogen bonding held in Ljubljana, Yugoslavia, there were studies of hydrogen-bonded complexes of phenols by neutron diffraction, infrared and electronic spectrometry.[71] Phenols are classed as well-recognized hydrogen-bonding acids and hydrogen-bonding bases by Pimentel and McClellan (1960).[71] Phenols form stronger hydrogen bonds than aliphatic alcohols because of the increase in electronegativity of the oxygen atom resulting from the lone pair of electron donation of the OH group to the aromatic ring. Phenols and substituted phenols can form intramolecular and intermolecular hydrogen bonds. The three dimensional structure of crystalline resorcinol (1,3-dihydroxybenzene) shows the intramolecular ---OH---OH--- hydrogen bonds. Many other *ortho*-substituted phenols e.g. o-nitrophenol or o-hydroxyacetophenone are listed as substances forming strong intramolecular hydrogen bonds.[71] Phenols are frequently used as convenient model proton donors in the study of intermolecular hydrogen bonded systems. Differently substituted phenols are characterized by a range of different acidities, and complexes can be studied with a wide variety of proton acceptors. The most commonly adopted acceptors are O and N bases. An example of intermolecular hydrogen bonding is the complex between phenol and benzonitrile where a hydrogen bond forms between phenolic OH and the π-electron system of the CN triple bond.[71]

## 1.9 Tautomeric equilibria

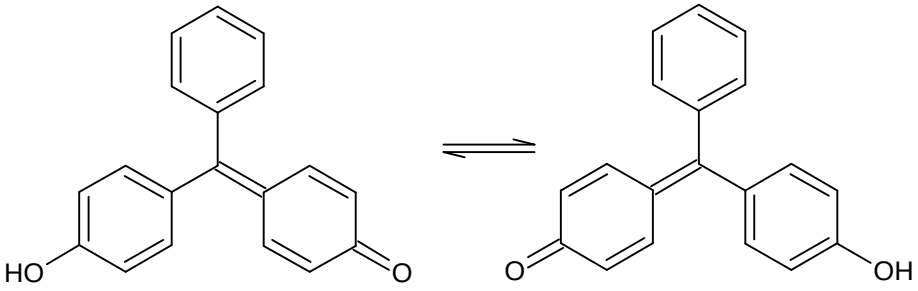
Tautomerism involving phenols is most often seen for Schiff bases, Mannich bases, or o-hydroxyazo aromatics, but is also observed in o-hydroxynitroso compounds. This is a relatively seldom occurrence for phenols not having nitrogen-containing substituents. The o- and p-nitrosophenols are tautomeric with o- and p-benzoquinone oxime, respectively. Some of the nitrosonaphthols are tautomers of naphthoquinone oximes.[71] The o- and p-nitrosophenol enjoy the possibility of resonance stabilization by π-electron donation from the phenolic hydroxyl group to

the nitroso group, and the o-isomer could also be stabilized by an intramolecular hydrogen bond. The tautomeric composition in solution is very much dependent on the compound's structure and solvent polarity. Various nitrosophenols, 1-nitroso-2-naphthol and 4-nitrosonaphthol exist exclusively as quinone oximes in the solid state. The tautomerism of 4-nitrosophenol/benzoquinone mono oxime is illustrated as follows:




**1** **2**

Benzaurins and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-ones **41**, **42** are a new type of tautomeric species showing intermolecular exchange.[71]




**41** **42**

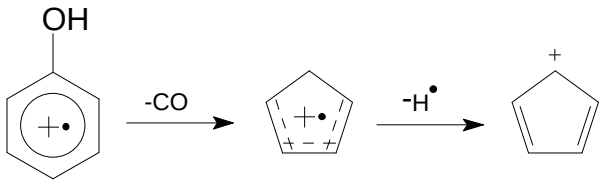
## 1.10 Mass spectrometry of phenols

Considerable use is made in this work from the information derived from the mass spectrometric analysis of reaction mixtures. It was therefore thought prudent to provide a brief overview of the more relevant aspects of the behaviour of phenolic compounds when subjected to gas phase mass spectrometric analysis.

Phenols are electron-rich aromatic compounds, and hence the chemical behaviour of phenolic ions in the gas phase, and the mass spectrometric information resulting from it, are characterized by the relatively facile formation of stable (albeit reactive) radical cations, protonated and cationic molecules, as well as more complex ionic adducts.

The ionization potential of phenol (IE = 8.5eV) and simple alkylphenols by removal of a single electron leads to the formation of the corresponding radical cations and require energies in the range of 8.5 – 7.8 eV (820 – 750 kJ $mol^{-1}$).[72,73] The hydroxyl group in the radical cations of phenols strongly facilitates the formation of transient intermediates and fragment ions whose structures correspond to ionized or protonated cyclohexadienones, quinomethanes, or quinones.

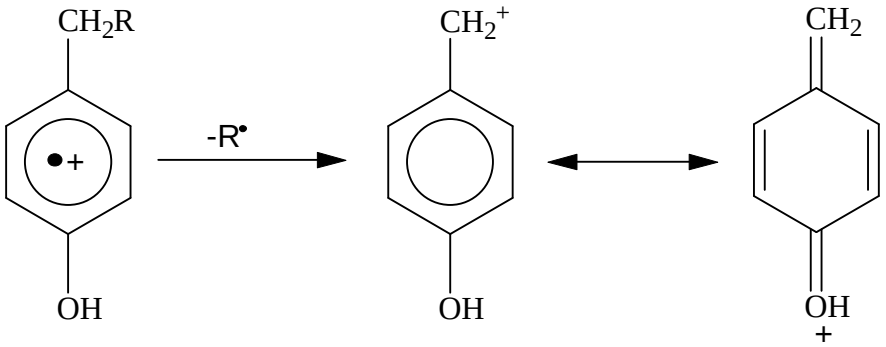
The fragmentation path of the parent phenol radical (Scheme 21) is very characteristic with the expulsion of CO to produce $C_5H_6^{\bullet+}$ ions with m/z = 66. Subsequent loss of $H^{\bullet}$ to give $C_5H_5^{+}$ ions is a common secondary fragmentation.




m/z=94 m/z=66 m/z=65

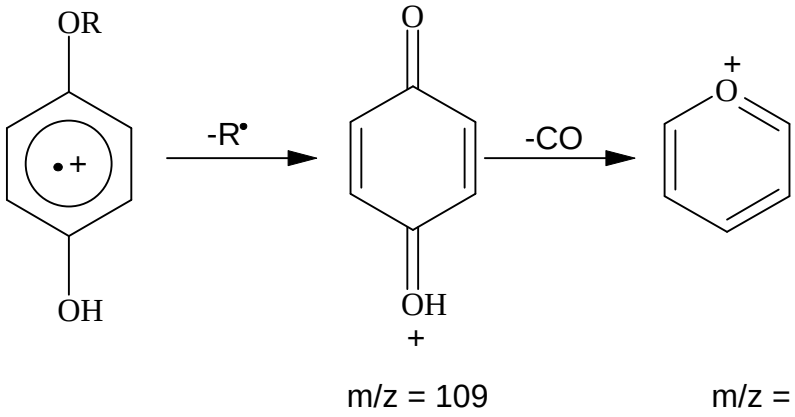
**Scheme-21: Fragmentation of the phenol radical cation**

If an aliphatic or alicyclic group is attached to the phenol ring, another typical fragmentation occurs namely benzylic cleavage resulting in the formation of the very characteristic fragment with m/z=107 (Scheme 22).[74,75] This fragmentation pathway is particularly facile when the aliphatic group is positioned *ortho* or *para* to the hydroxyl group, or when the phenol contains an α-branched side chain (since the $HOC_6H_4CH^+R$ benzylic ions are even more stable than the primary ones).




**Scheme-22: Fragmentation via benzylic cleavage**

In the case of monoalkyl ethers of hydroquinone (and catechol), initial loss of the alkyl group (to form the protonated *p*- or *o*-cyclohexadienone with the very characteristic fragment with m/z = 109), is followed by loss of CO leading to the formation of the energetically favourable pyranylium ion (Scheme 23).




**Scheme-23: Fragmentation of mono-alkyl ethers of hydroquinone/catechol**

# CHAPTER 2

## RESULTS AND DISCUSSION

### 2.1 Introduction

In previous work done in our laboratories,[1] a method was elaborated to produce phenolic mono-ethers in a simple one-pot process. In these procedures, when 4-hydroxyacetophenone was treated with ammonium peroxy-disulphate in an alcohol as reaction solvent and in the presence of concentrated sulphuric acid or other strong protonic acids, 4-alkoxyphenol resulted as a product in good to excellent yield. It was suggested during the course of these investigations that the main route to the observed 4-alkoxyphenols was as a result of the substitution of an alkoxy-group on a hydroquinone-benzoquinone complex (quinhydrone). Since this method provides a very convenient way to produce various phenol mono-ethers, it was of interest to study the general scope of the reaction (substrates that can be used as well as nucleophiles that can be used for substituting the position *para*- to the hydroxyl group). Of particular interest was to investigate the reaction of 4-nitrosophenol with alcohols in the presence of hydroquinone/benzoquinone since the 4-nitrosophenol exists as an equilibrium mixture of oxime form (keto or quinone form) and nitroso form (enol from) in solution and could interact with both hydroquinone and benzoquinone in a manner similar as does hydroquinone and benzoquinone. Other possible compounds of interest for this type of reaction include 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one-type compounds. The investigation of the reaction mechanism at work during these substitution reactions was of particular interest to this study.

## 2.2 Blank reactions: Substrate and acid catalyst

In order to investigate whether the presence of hydroquinone is required to form 4-methoxyphenol when benzoquinone, or 4-nitrosophenol, or 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one is reacted with methanol in the presence of an acid catalyst, several reactions were carried out where benzoquinone (in the absence of hydroquinone) was reacted with methanol in the presence of sulphuric acid. In addition, the reverse reaction between hydroquinone (in the absence of benzoquinone) and methanol in the presence of acid catalyst was also investigated.

### 2.2.1 Hydroquinone

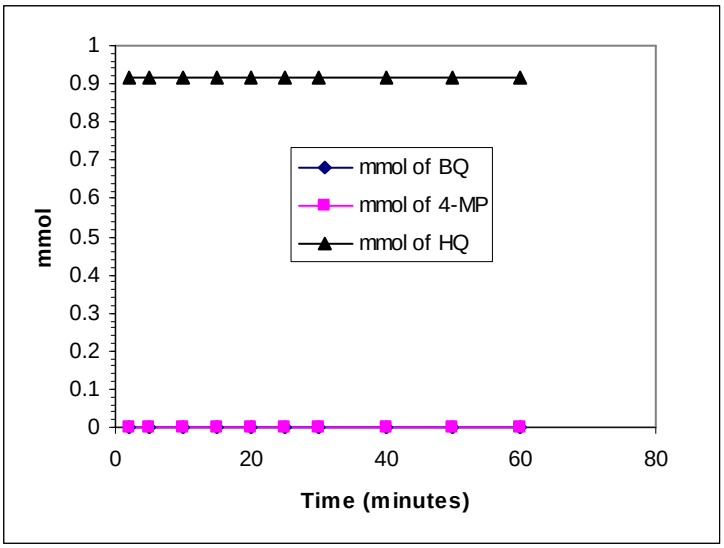
In this reaction, 0.916 mmol (0.1002g) of hydroquinone was reacted with methanol (20mL) to which was added 0.0512g of concentrated $H_2SO_4$ (18M). The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.1 and Figure 2.1) show that no reaction takes place under these reaction conditions.

**Table 2.1: Blank hydroquinone reaction**

| Time (minutes) | BQ* (mmol) | HQ** (mmol) | 4-MP*** (mmol) |
|---|---|---|---|
| 2 | 0 | 0.916 | 0 |
| 5 | 0 | 0.916 | 0 |
| 10 | 0 | 0.916 | 0 |
| 15 | 0 | 0.916 | 0 |
| 20 | 0 | 0.916 | 0 |
| 25 | 0 | 0.916 | 0 |
| 30 | 0 | 0.916 | 0 |
| 40 | 0 | 0.916 | 0 |
| 50 | 0 | 0.916 | 0 |
| 60 | 0 | 0.916 | 0 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.1: Blank hydroquinone reaction**




## 2.2.2 Benzoquinone

In this reaction, 0.91 mmol (0.0984g) of benzoquinone was reacted with methanol (20mL) to which 0.0512g of concentrated $H_2SO_4$ (18M) was added. The reaction was also carried out at reflux temperature of methanol ($64^0$C). In the initial reaction that was carried out, benzoquinone was used "as is" as supplied by Aldrich (98%) and small amounts of 4-methoxyphenol were found at the end of reaction (60 minutes) (Figure 2.2). The GC trace of the "Time zero" aliquot, however, shows the presence of small amounts of hydroquinone (Figure 2.3) (confirmed by NMR analysis) and hence this reaction could not be interpreted as a "blank" reaction.

**Figure 2.2: GC trace of the "as is" benzoquinone blank reaction**

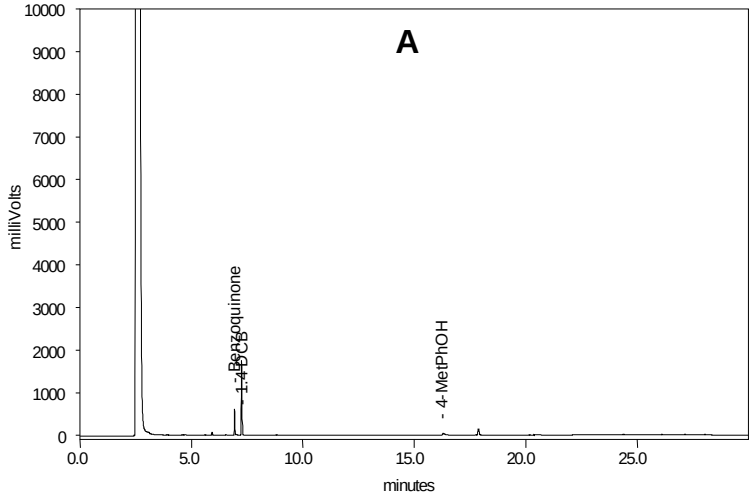
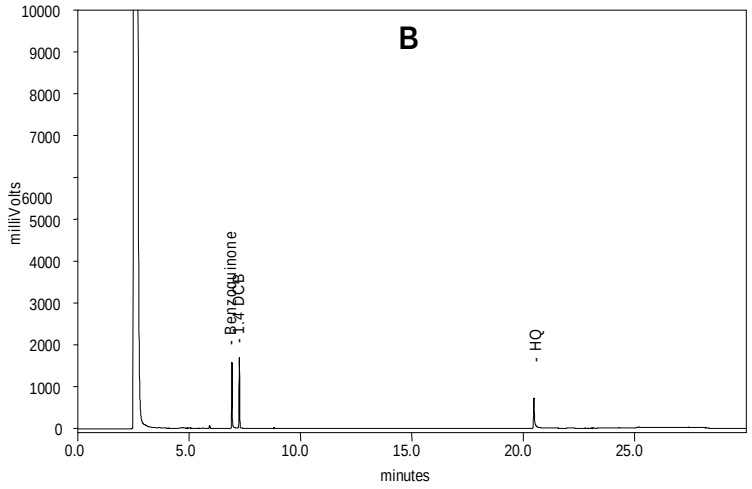


**Figure 2.3: GC trace at time zero of the "as is" benzoquinone blank reaction**




In order to observe whether benzoquinone would undergo any reaction with methanol under the specified reaction conditions, the "as is" benzoquinone was purified by column chromatography. When the purified benzoquinone (Figure 2.4) was reacted with methanol in the presence of concentrated sulphuric acid under similar reaction conditions, no 4-methoxyphenol was formed as indicated by the GC trace of the reaction mixture after 60 minutes (Figure 2.5).

**Figure 2.4: GC trace of purified benzoquinone**

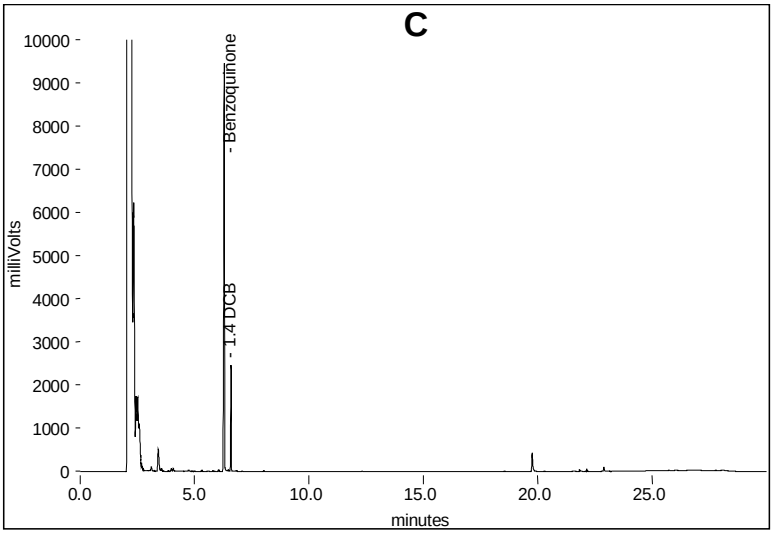
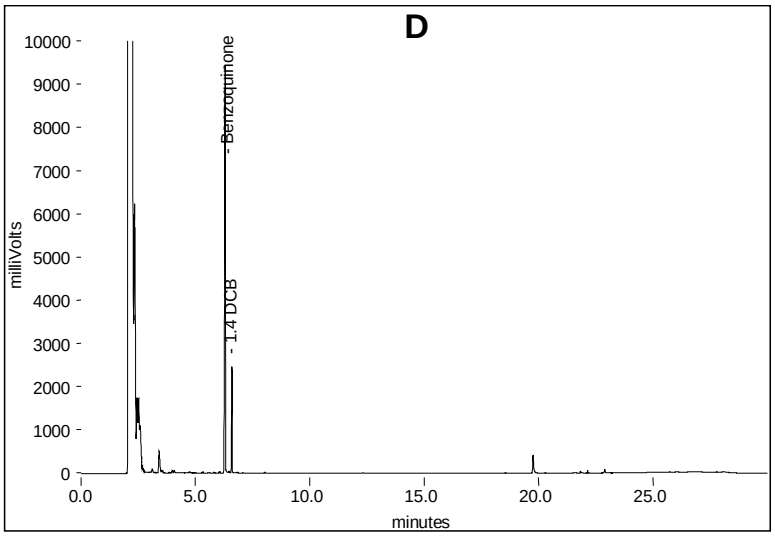


**Figure 2.5: GC trace of blank reaction with purified benzoquinone**




The results obtained from these blank reactions clearly demonstrate that neither hydroquinone, nor benzoquinone react with an alcohol (methanol) in the presence of concentrated sulphuric acid to give 4-methoxyphenol. When, however, a small amount of hydroquinone is present in the benzoquinone, 4-methoxyphenol is rapidly formed under the reaction conditions.

### 2.2.3 4-Nitrosophenol

In this reaction, 0.812 mmol (0.100g) of 4-nitrosophenol was reacted with methanol (20mL) to which was added 0.519 mmol (0.0512g) of concentrated $H_2SO_4$ (18M). The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.2 and Figure 2.7) show that a large amount of 4-nitrosoanisole formed under these reaction conditions, but no 4-methoxyphenol formation takes place as indicated by the GC trace of the reaction mixture after 2 hours (Figure 2.6).

**Figure 2.6: GC trace of blank reaction of 4-nitrosophenol**

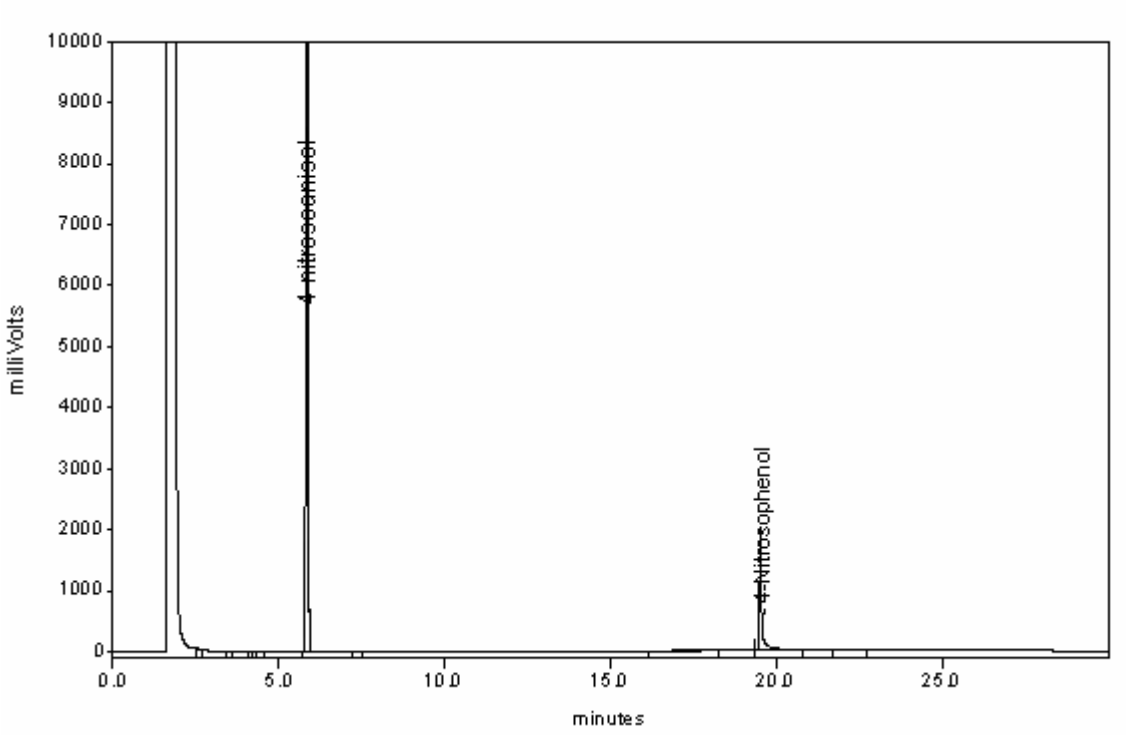
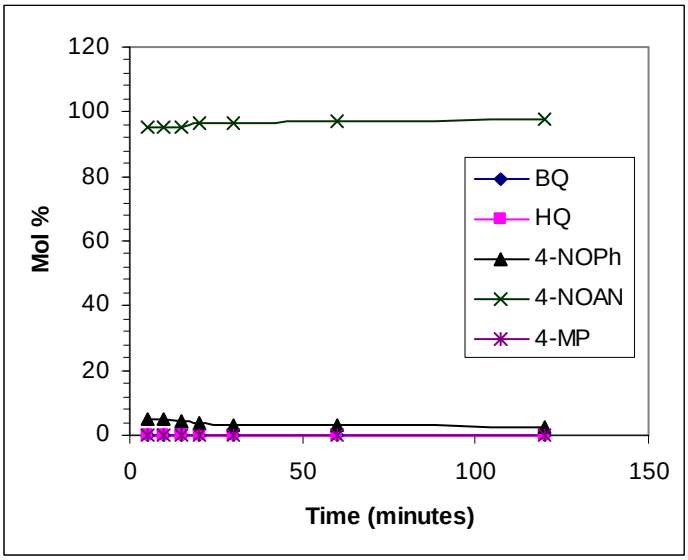



**Table 2.2: Blank 4-nitrosophenol reaction**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-NOPh*** (Mol %) | 4-NOAN**** (Mol %) | 4-MP***** (Mol %) |
|---|---|---|---|---|---|
| 5 | 0 | 0 | 5 | 95 | 0 |
| 10 | 0 | 0 | 4.9 | 95.1 | 0 |
| 15 | 0 | 0 | 4.6 | 95.4 | 0 |
| 20 | 0 | 0 | 3.8 | 96.2 | 0 |
| 30 | 0 | 0 | 3.2 | 96.8 | 0 |
| 60 | 0 | 0 | 3.1 | 96.9 | 0 |
| 120 | 0 | 0 | 2.3 | 97.7 | 0 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-NOPh= 4-nitrosophenol; ****4-NOAN= 4-nitrosoanisole; *****4-MP= 4-methoxyphenol

**Figure 2.7: Blank 4-nitrosophenol reaction**




### 2.2.4 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one

In this reaction, 0.362 mmol (0.100g) of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one was reacted with methanol (20mL) to which 0.519 mmol (0.0512g) of concentrated $H_2SO_4$ (18M) was added. The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.3 and Figure 2.9) show that a large amount of 1-(diphenylmethyl)-4-methoxybenzene formed but no 4-methoxyphenol formation occurred under these reaction conditions as indicated by the GC trace of the reaction mixture after 2 hours (Figure 2.8).

**Figure 2.8: GC trace of blank reaction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one**

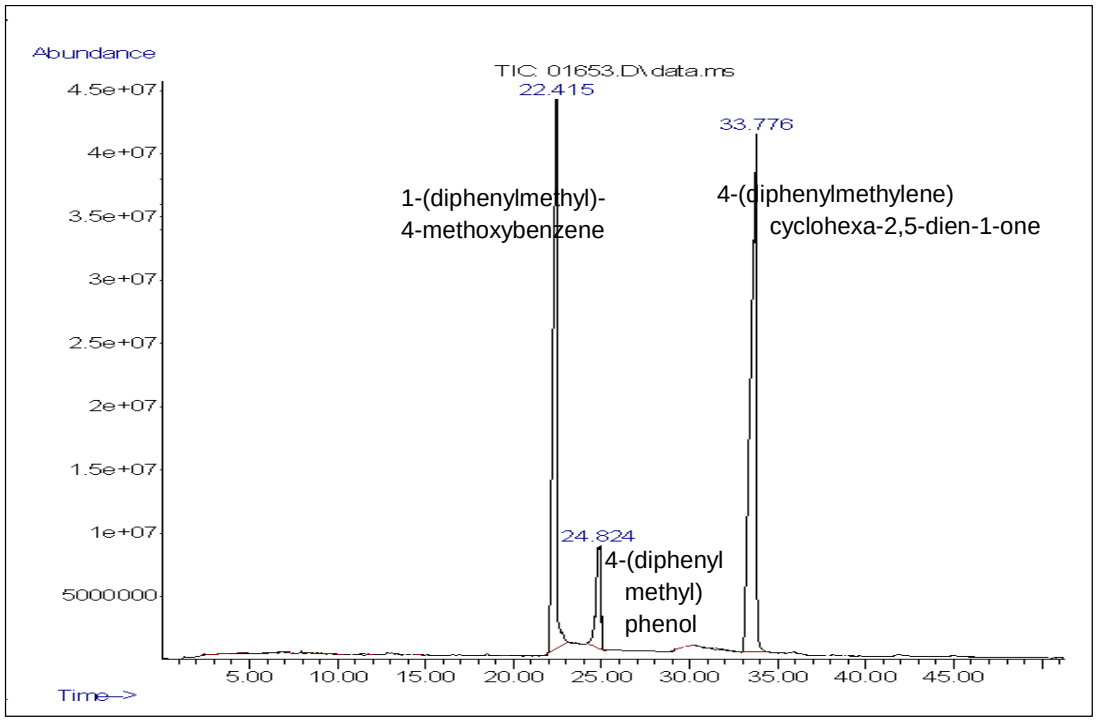
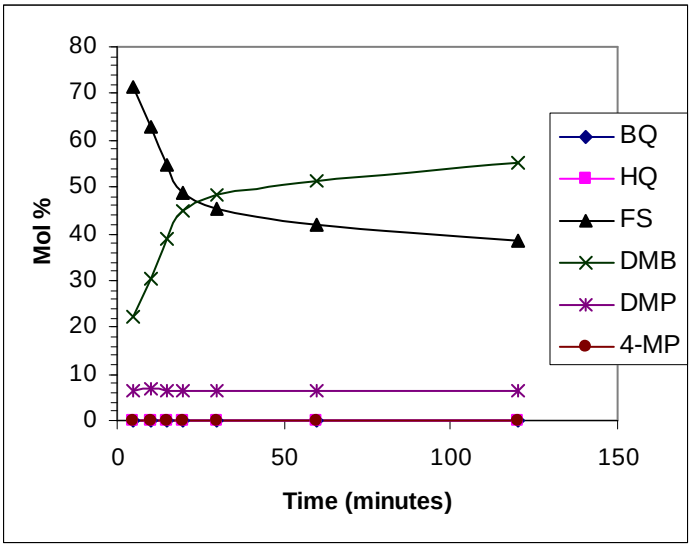



**Table 2.3: Blank 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one reaction**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | FS*** (Mol %) | DMB**** (Mol %) | DMP***** (Mol %) | 4-MP****** (Mol %) |
|---|---|---|---|---|---|---|
| 5 | 0 | 0 | 71.4 | 22.1 | 6.5 | 0 |
| 10 | 0 | 0 | 63.1 | 30.2 | 6.7 | 0 |
| 15 | 0 | 0 | 54.6 | 38.9 | 6.5 | 0 |
| 20 | 0 | 0 | 48.8 | 44.8 | 6.4 | 0 |
| 30 | 0 | 0 | 45.2 | 48.5 | 6.3 | 0 |
| 60 | 0 | 0 | 42.1 | 51.4 | 6.5 | 0 |
| 120 | 0 | 0 | 38.3 | 55.3 | 6.4 | 0 |

*BQ= benzoquinone; **HQ= hydroquinone; ***FS= 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one; ****DMB= 1-(diphenylmethyl)-4-methoxybenzene; *****DMP= 4-(diphenylmethyl)phenol; ******4-MP= 4-methoxyphenol

**Figure 2.9: Blank 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one reaction**




### 2.2.5 Hydroquinone + benzoquinone: No acid catalyst

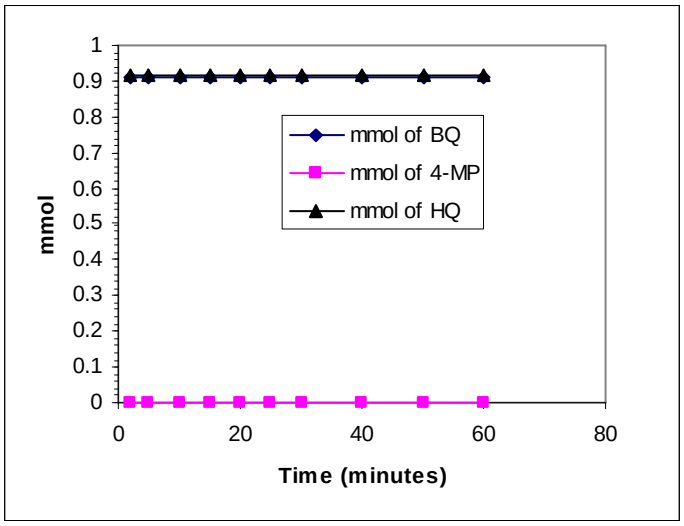
In this reaction, 0.916 mmol (0.1002g) of hydroquinone and 0.912 mmol (0.0984g) of benzoquinone were reacted with methanol (20mL) but in the absence of $H_2SO_4$. The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.4 and Figure 2.10) show that no reaction takes place under these reaction conditions. This reaction clearly demonstrated that in the absence of sulphuric acid, hydroquinone-benzoquinone does not afford 4-methoxyphenol formation.

**Table 2.4: Hydroquinone + benzoquinone: No sulphuric acid**

| Time (minutes) | BQ* (mmol) | HQ** (mmol) | 4-MP*** (mmol) |
|---|---|---|---|
| 2 | 0.912 | 0.916 | 0 |
| 5 | 0.912 | 0.916 | 0 |
| 10 | 0.912 | 0.916 | 0 |
| 15 | 0.912 | 0.916 | 0 |
| 20 | 0.912 | 0.916 | 0 |
| 25 | 0.912 | 0.916 | 0 |
| 30 | 0.912 | 0.916 | 0 |
| 40 | 0.912 | 0.916 | 0 |
| 50 | 0.912 | 0.916 | 0 |
| 60 | 0.912 | 0.916 | 0 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.10: Hydroquinone + benzoquinone: No sulphuric acid**



### 2.2.6 4-Nitrosophenol + Hydroquinone: No acid catalyst

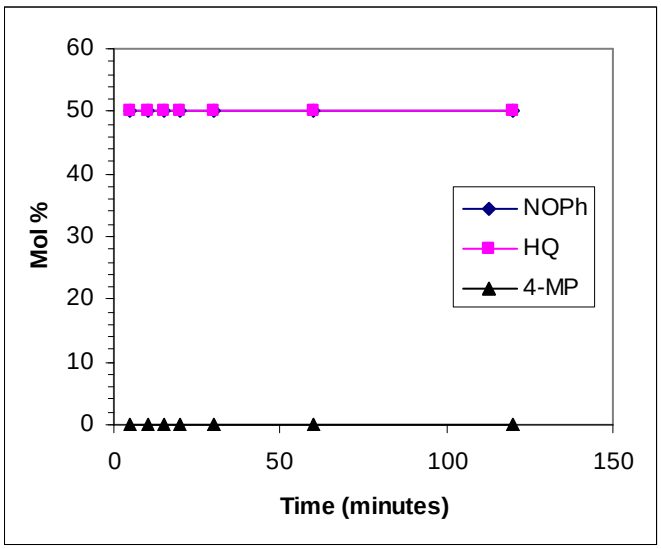
In this reaction, 0.812 mmol (0.100g) of 4-nitrosophenol and 0.812 mmol (0.0894g) of hydroquinone were reacted with methanol (20mL) but in the absence of $H_2SO_4$. The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.5 and Figure 2.11) show that no reaction takes place under these reaction conditions. This reaction clearly demonstrated that in the absence of sulphuric acid, 4-nitrosophenol-hydroquinone does not afford 4-methoxyphenol formation.

**Table 2.5: 4-Nitrosophenol + hydroquinone: No sulphuric acid**

| Time (minutes) | NOPh* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 5 | 50 | 50 | 0 |
| 10 | 50 | 50 | 0 |
| 15 | 50 | 50 | 0 |
| 20 | 50 | 50 | 0 |
| 30 | 50 | 50 | 0 |
| 60 | 50 | 50 | 0 |
| 120 | 50 | 50 | 0 |

*NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.11: 4-Nitrosophenol + hydroquinone: No sulphuric acid**



### 2.2.7 4-Nitrosophenol + Benzoquinone: No acid catalyst

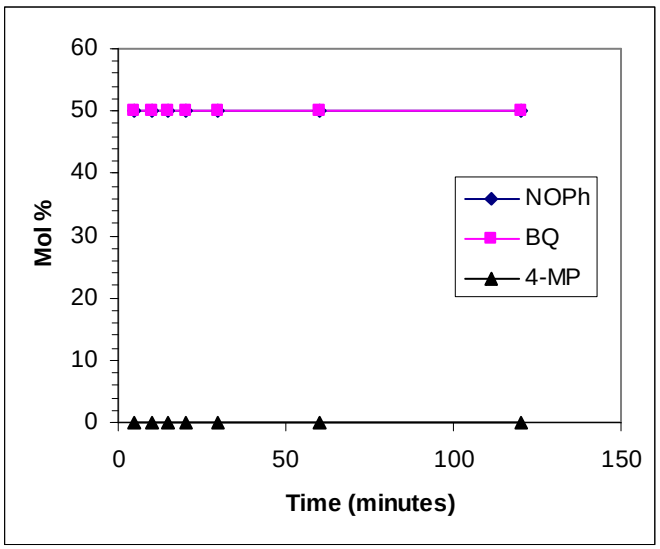
In this reaction, 0.812 mmol (0.100g) of 4-nitrosophenol and 0.812 mmol (0.0878g) of benzoquinone were reacted with methanol (20mL) but in the absence of $H_2SO_4$. The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.6 and Figure 2.12) show that no reaction takes place under these reaction conditions. This reaction clearly demonstrated that in the absence of sulphuric acid, 4-nitrosophenol-benzoquinone does not afford 4-methoxyphenol formation.

**Table 2.6: 4-Nitrosophenol + benzoquinone: No sulphuric acid**

| Time (minutes) | NOPh* (Mol %) | BQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 5 | 50 | 50 | 0 |
| 10 | 50 | 50 | 0 |
| 15 | 50 | 50 | 0 |
| 20 | 50 | 50 | 0 |
| 30 | 50 | 50 | 0 |
| 60 | 50 | 50 | 0 |
| 120 | 50 | 50 | 0 |

*NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-MP= 4-methoxyphenol

**Figure 2.12: 4-Nitrosophenol + benzoquinone: No sulphuric acid**



### 2.2.8 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one + Hydroquinone: No acid catalyst

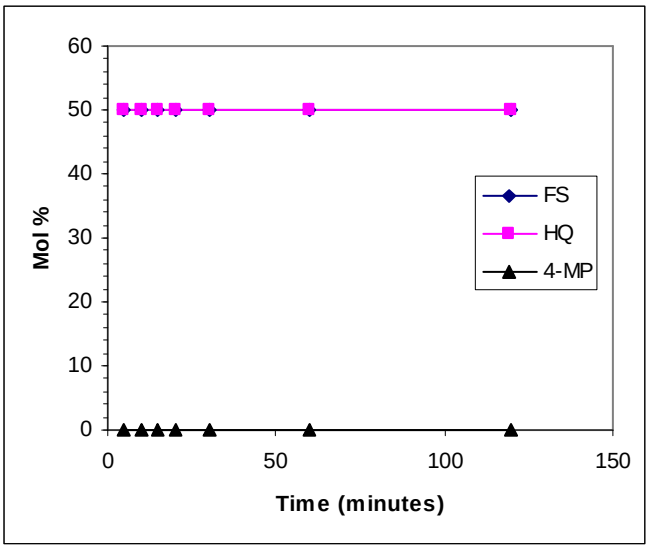
In this reaction, 0.362 mmol (0.100g) of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and 0.362 mmol (0.0399g) of hydroquinone were reacted with methanol (20mL) but in the absence of $H_2SO_4$. The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.7 and Figure 2.13) show that no reaction takes place under these reaction conditions. This reaction clearly demonstrated that in the absence of sulphuric acid, 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one-hydroquinone does not afford 4-methoxyphenol formation.

**Table 2.7: 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one + hydroquinone: No sulphuric acid**

| Time (minutes) | FS* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 5 | 50 | 50 | 0 |
| 10 | 50 | 50 | 0 |
| 15 | 50 | 50 | 0 |
| 20 | 50 | 50 | 0 |
| 30 | 50 | 50 | 0 |
| 60 | 50 | 50 | 0 |
| 120 | 50 | 50 | 0 |

*FS= 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.13: 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one + hydroquinone: No sulphuric acid**




### 2.2.9 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one + Benzoquinone: No acid catalyst

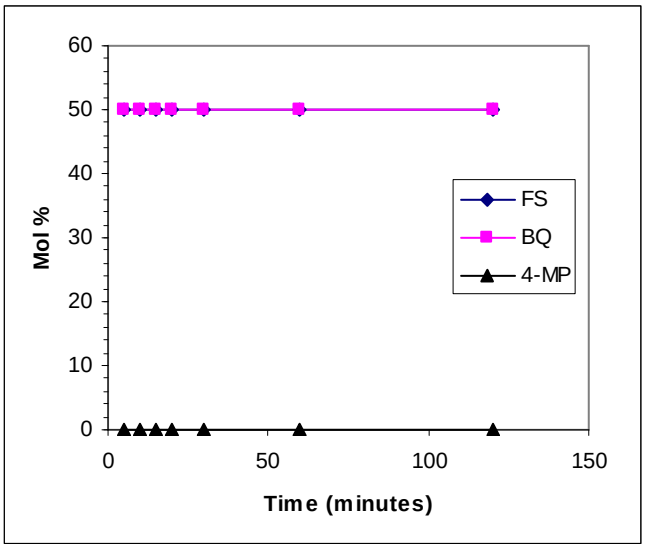
In this reaction, 0.362 mmol (0.100g) of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and 0.362 mmol (0.0392g) of benzoquinone were reacted with methanol (20mL) but in the absence of $H_2SO_4$. The reaction was carried out at the reflux temperature of methanol ($64^0$C). Aliquots of the reaction mixture were removed at regular intervals and analyzed by gas chromatography as described in Section 3.4.1. The results obtained (Table 2.8 and Figure 2.14) show that no reaction takes place under these reaction conditions. This reaction clearly demonstrated that in the absence of sulphuric acid, 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one-benzoquinone does not afford 4-methoxyphenol formation.

**Table 2.8: 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one + benzoquinone: No sulphuric acid**

| Time (minutes) | FS* (Mol %) | BQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 5 | 50 | 50 | 0 |
| 10 | 50 | 50 | 0 |
| 15 | 50 | 50 | 0 |
| 20 | 50 | 50 | 0 |
| 30 | 50 | 50 | 0 |
| 60 | 50 | 50 | 0 |
| 120 | 50 | 50 | 0 |

*FS= 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one; **BQ= benzoquinone; ***4-MP= 4-methoxyphenol

**Figure 2.14: 4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one + benzoquinone: No sulphuric acid**



## 2.3 Investigation of the hydroquinone:benzoquinone reaction with methanol

### 2.3.1 Hydroquinone:benzoquinone: Effect of mole ratios

In order to study the effect of the hydroquinone:benzoquinone mole ratio on the rate and extent of formation of 4-methoxyphenol during the reaction of hydroquinone/benzoquinone mixtures with methanol in the presence of sulphuric acid as the acid catalyst, several experiments were carried out in which the respective amounts of hydroquinone and benzoquinone were varied relative to each other. During these reactions the total amount of hydroquinone was kept constant at about 0.9 mmol and the amount of benzoquinone in the reaction mixture was reduced from 0.9 mmol to 0.45 mmol, to 0.18 mmol and finally to 0.09 mmol to give approximate hydroquinone:benzoquinone ratios of 1:1, 2:1, 5:1 and 10:1. The amount of acid catalyst (0.051g; 0.519 mmol) and the amount of methanol (20 mL) were kept constant in all the reactions, which were all carried out at a reaction temperature of $64^0$C. The results of these experiments are summarised in Tables 2.9 – 2.12, and illustrated graphically in Figures 2.16 – 2.19. In these reactions, no side product formation takes place under these reaction conditions, as indicated by the GC trace of the reaction mixture after 5 minutes reaction time (Figure 2.15).

**Table 2.9: HQ:BQ, Mole ratio = 1:1**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50.0 | 50.0 | 0 |
| 2 | 41.8 | 19.8 | 38.3 |
| 5 | 23.1 | 5.5 | 71.4 |
| 10 | 7.0 | 2.2 | 90.9 |
| 15 | 1.3 | 0 | 98.7 |
| 20 | 0 | 0 | 100 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.10: HQ:BQ, Mole ratio = 2:1**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 33.3 | 66.6 | 0 |
| 2 | 26.8 | 43.0 | 30.2 |
| 5 | 20.7 | 23.7 | 55.6 |
| 10 | 12.4 | 16.0 | 71.5 |
| 15 | 6.8 | 13.4 | 79.8 |
| 20 | 2.6 | 8.4 | 89.0 |
| 30 | 0 | 5.4 | 94.6 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.11: HQ:BQ, Mole ratio = 5:1**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 16.6 | 83.3 | 0 |
| 2 | 11.7 | 66.9 | 21.4 |
| 5 | 8.1 | 56.8 | 35.0 |
| 10 | 3.6 | 46.7 | 49.7 |
| 15 | 0 | 40.8 | 59.2 |
| 20 | 0 | 33.9 | 66.1 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.12: HQ:BQ, Mole ratio = 10:1**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 9.0 | 90.9 | 0 |
| 2 | 4.3 | 85.3 | 10.4 |
| 5 | 2.5 | 75.2 | 22.3 |
| 10 | 3.6 | 67.3 | 29.1 |
| 15 | 1.2 | 63.5 | 35.2 |
| 20 | 0 | 59.0 | 41.0 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.15: GC trace of HQ:BQ, Mole ratio=1:1**

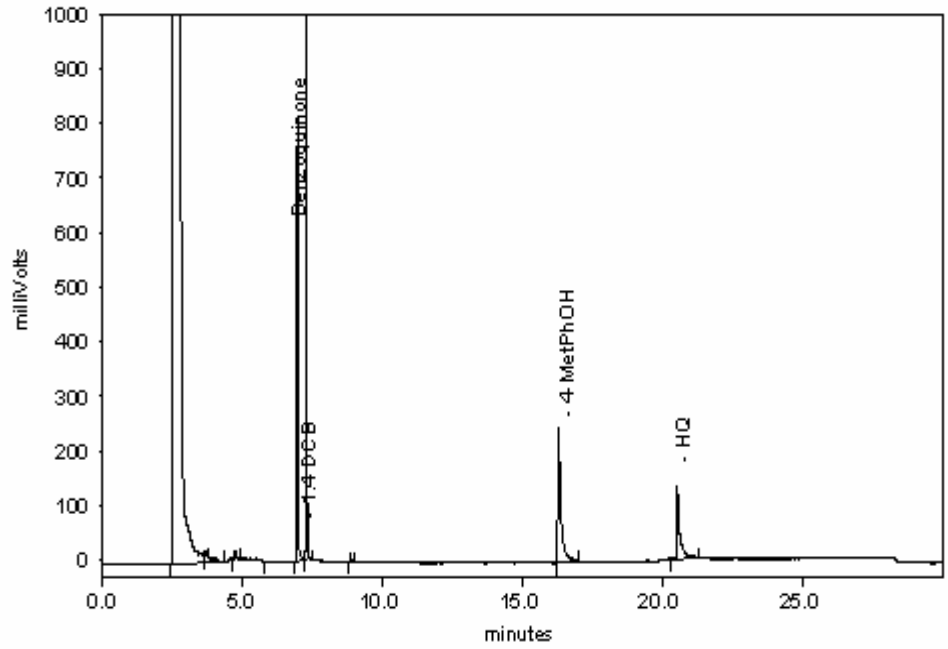



**Figure 2.16: HQ:BQ (1:1 Mol)**

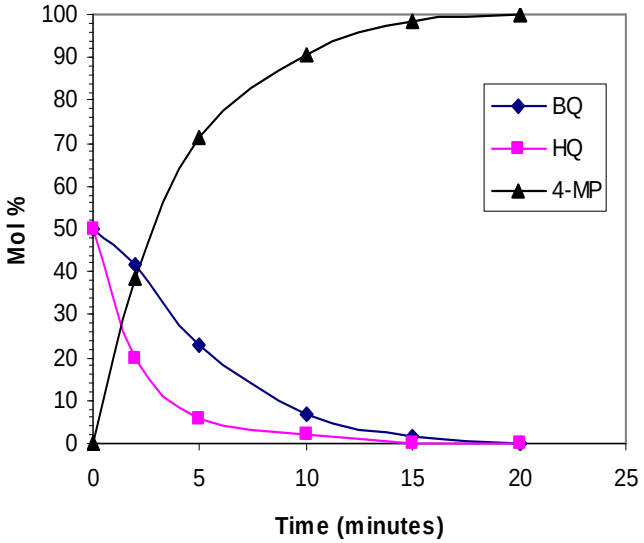



**Figure 2.17: HQ:BQ (2:1 Mol)**

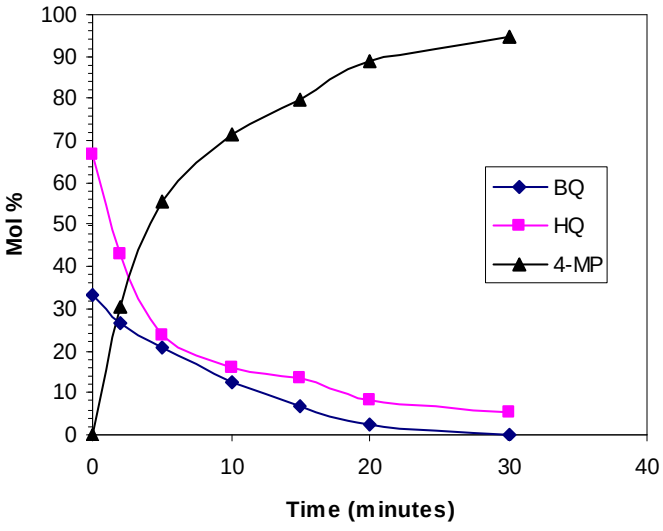


**Figure-2.18: HQ:BQ (5:1 Mol)**

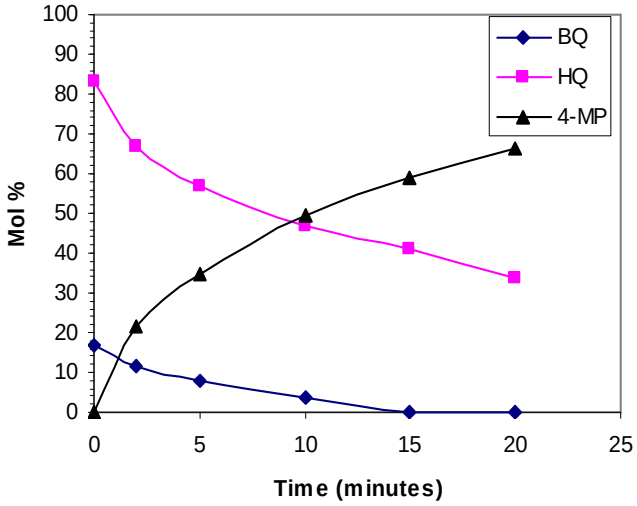
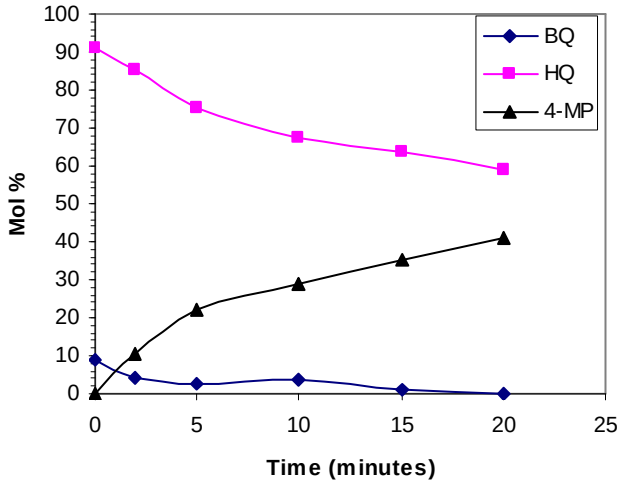



**Figure-2.19: HQ:BQ (10:1 Mol)**




The following observations from the above results are worth noting:

1) ***Rate of reaction:*** The comparisons in Figures 2.16 - 2.19 show that the initial rate of reaction is higher in those reactions where the hydroquinone:benzoquinone mol ratio approaches 1:1. This observation is clearly illustrated by comparing the initial rates of substrate disappearance and product formation (Table 2.9). These rates were calculated from the slopes of the substrate disappearance/product appearance curves over the first three minutes of each reaction and are given in Table 2.13.

**Table-2.13: Reaction rates for substrate consumption and 4-methoxyphenol formation**

| Mol ratio (HQ:BQ) | $R_1$[a] BQ ($x10^{-2}$) | $R_2$[b] HQ ($x10^{-2}$) | $R_3$[c] 4-MP ($x10^{-2}$) |
|---|---|---|---|
| 1:1 | -9.81 | -21.98 | 32.11 |
| 2:1 | -3.51 | -12.46 | 16.16 |
| 5:1 | -2.02 | -7.15 | 9.28 |
| 10:1 | -1.32 | -3.04 | 4.37 |

[a] - Rate of benzoquinone consumption, mmol $min^{-1}$, [b] - Rate of hydroquinone consumption, mmol $min^{-1}$, [c] - Rate of 4-methoxyphenol formation, mmol $min^{-1}$

2) ***Reaction stoichiometry:*** A number of aspects regarding the results reflected above with respect to the stoichiometry of the reaction are worth noting:

   (a) The yield of 4-methoxyphenol (calculated as the percentage of 4-methoxyphenol formed relative to the sum of the initial amounts of hydroquinone and benzoquinone used) is much higher in reactions where the HQ:BQ mole ratio approaches 1:1 compared to reactions in which the mole ratios are decreased to 5:1 and lower.

   (b) Despite this decrease in the yield of 4-methoxyphenol, it is important to note that the ratio in which 4-methoxyhenol is formed relative to the amount of benzoquinone initially added in the reaction mixture increases as the mole ratio of hydroquinone:benzoquinone increases. This implies that benzoquinone reacts with more than one equivalent of hydroquinone to form the product, 4-methoxyphenol. This is clearly seen from the comparison in Table 2.14 where the ratio:

$$\textit{Mole ratio} = \frac{\textit{Amount of 4-methoxyphenol after 20 minutes}}{\textit{Amount of benzoquinone initially added}} \; \textit{X 100}$$

   is shown against the initial mole ratio of hydroquinone:benzoquinone initially added.

**Table 2.14: Ratio of 4-alkoxyphenol/benzoquinone**

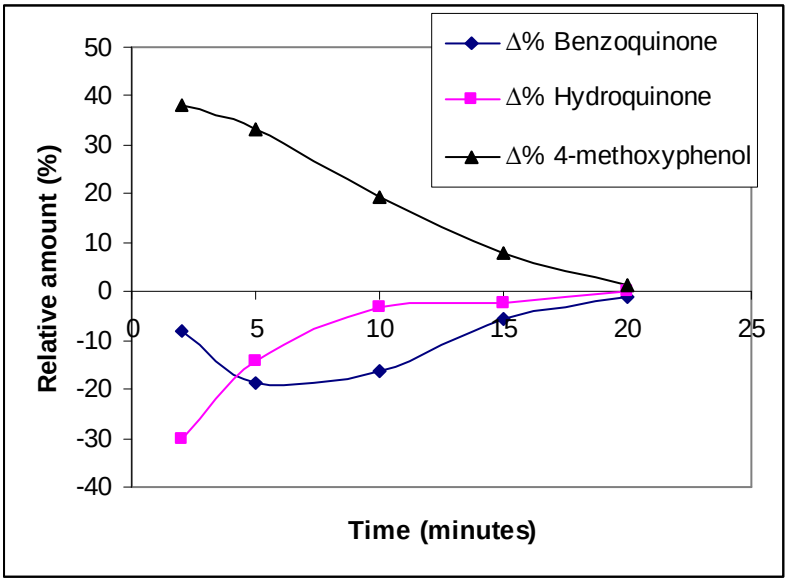
| Mol ratio (HQ:BQ) | Mol ratio (4-MP/BQ) |
|---|---|
| 1:1 | 2 |
| 2:1 | 2.838 |
| 5:1 | 3.966 |
| 10:1 | 4.51 |

(c) The rate of hydroquinone consumption is initially faster than benzoquinone consumption as can be observed by comparing the amount of hydroquinone or benzoquinone consumed at different time intervals. Table 2.15 and Figure 2.20 show the comparison of the change in the amounts of hydoquinone, benzoquinone and 4-methoxyphenol against reaction time for the reaction where the hydroquinone:benzoquinone ratio used was 1:1.

**Table 2.15: Comparison of rates of hydroquinone, benzoquinone consumption, and 4-methoxyphenol formation versus time**

| Reaction Time (Minutes) | Δ% Benzoquinone | Δ% Hydroquinone | Δ% 4-methoxyphenol |
|---|---|---|---|
| 2 | -8.2 | -30.2 | 38.3 |
| 5 | -18.7 | -14.3 | 33.1 |
| 10 | -16.1 | -3.3 | 19.5 |
| 15 | -5.7 | -2.2 | 7.8 |
| 20 | -1.3 | 0 | 1.3 |

**Figure 2.20: Plot of the change in component amounts versus time**



The above considerations strongly suggest that the reaction between benzoquinone/hydroquinone and methanol does not require benzoquinone in a 1:1 ratio with hydroquinone to form the 4-methoxyphenol product.

Extending the reaction time from 20 minutes to 300 minutes (Tables 2.16 – 2.17 and Figures 2.21 – 2.22) for the reactions where high hydroquinone:benzoquinone ratios were used has no effect on either the yield of 4-methoxyphenol formed, nor the final molar ratio of 4-methoxyphenol/benzoquinone. Again it is important to note that in these reactions, there is no benzoquinone left after 20 minutes. Therefore it is clear that without benzoquinone, hydroquinone cannot afford the formation of 4-methoxyphenol.

**Table 2.16: HQ:BQ ratio = 5:1 (Reaction time= 5hours)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 16.6 | 83.3 | 0 |
| 10 | 2.9 | 47.7 | 49.4 |
| 20 | 0 | 34.8 | 65.2 |
| 30 | 0 | 33.7 | 66.3 |
| 60 | 0 | 34.2 | 65.8 |
| 120 | 0 | 33.5 | 66.5 |
| 180 | 0 | 33.3 | 66.7 |
| 240 | 0 | 33.2 | 66.8 |
| 300 | 0 | 32.9 | 67.1 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.17: HQ:BQ ratio = 10:1 (Reaction time= 5hours)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 9.0 | 90.9 | 0 |
| 10 | 3.2 | 66.3 | 30.5 |
| 20 | 0 | 58.1 | 41.9 |
| 30 | 0 | 57.4 | 42.6 |
| 60 | 0 | 57.3 | 42.7 |
| 120 | 0 | 58.2 | 41.8 |
| 180 | 0 | 57.5 | 42.5 |
| 240 | 0 | 57.1 | 42.9 |
| 300 | 0 | 57.2 | 42.8 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.21: HQ:BQ ratio = 5:1 (RT= 5hrs)**

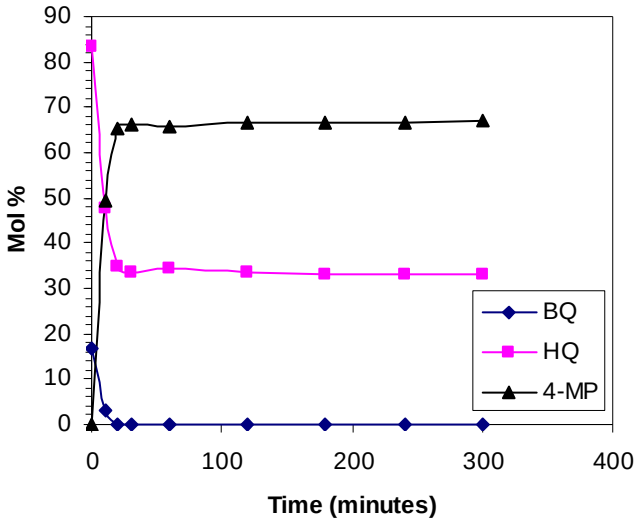
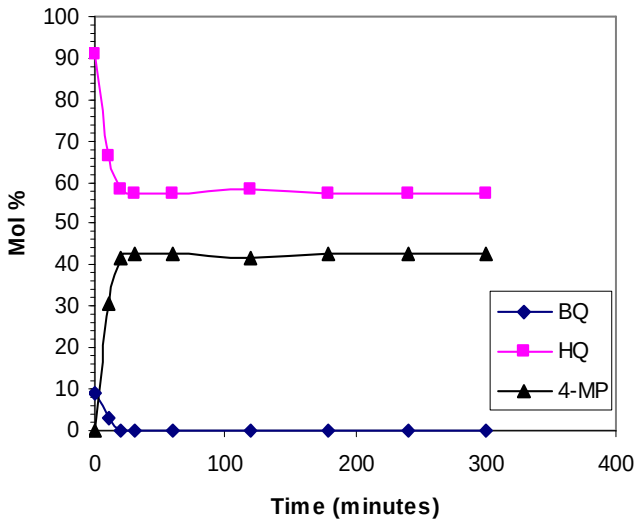



**Figure 2.22: HQ:BQ ratio = 10:1 (RT= 5hrs)**




### 2.3.2 Hydroquinone:benzoquinone: Effect of reaction temperature

In order to study the effect of the change in reaction temperature on the rate and extent of formation of 4-methoxyphenol during the reaction of hydroquinone/benzoquinone mixtures with methanol in the presence of sulphuric acid as the acid catalyst, three different experiments were carried out in which the reaction temperature was varied from reflux temperature ($64^0$C) to room

temperature. During these reactions the hydroquinone:benzoquinone mole ratio was kept constant at about 1:1 (0.9:0.9 mmol). The temperature was reduced from reflux temperature to $50^0$C, to $30^0$C and finally to room temperature. The amount of acid catalyst (0.051g; 0.519 mmol) and the amount of methanol (20 mL) were also kept constant in all the reactions. The results of these reactions are summarized in Tables 2.18 – 2.21, and illustrated graphically in Figures 2.23 – 2.26.

**Table 2.18: Reaction temperature = $64^0$C (reflux temperature)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50.0 | 50.0 | 0 |
| 2 | 41.8 | 19.8 | 38.3 |
| 5 | 23.1 | 5.5 | 71.4 |
| 10 | 7.0 | 2.2 | 90.9 |
| 15 | 1.3 | 0 | 98.7 |
| 20 | 0 | 0 | 100 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.19: Reaction temperature = $50^0$C**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 48.4 | 34.3 | 17.3 |
| 5 | 46.7 | 28.8 | 24.5 |
| 10 | 42 | 24.2 | 33.8 |
| 15 | 36.1 | 20 | 43.9 |
| 20 | 29.3 | 17.4 | 53.3 |
| 30 | 21.6 | 8.7 | 69.7 |
| 40 | 17.7 | 2.8 | 79.5 |
| 50 | 10.4 | 0 | 89.6 |
| 60 | 6.4 | 0 | 92.6 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.20: Reaction temperature = $30^0$C**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 48.6 | 40.5 | 10.9 |
| 5 | 46.7 | 36.9 | 16.4 |
| 10 | 45.2 | 33.1 | 21.7 |
| 15 | 44.3 | 29.9 | 25.8 |
| 20 | 43.1 | 26.4 | 30.5 |
| 30 | 41.7 | 18.9 | 39.4 |
| 40 | 38.6 | 11.9 | 49.5 |
| 50 | 36.8 | 8.1 | 55.1 |
| 60 | 33.4 | 5.1 | 61.5 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.21: Reaction temperature = room temperature**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 48.9 | 42.8 | 8.3 |
| 5 | 46.9 | 36.4 | 16.7 |
| 10 | 45.1 | 33.4 | 21.5 |
| 15 | 44.2 | 32.4 | 23.4 |
| 20 | 43.4 | 31 | 25.6 |
| 30 | 41.8 | 30.3 | 27.9 |
| 40 | 40.5 | 29.7 | 29.8 |
| 50 | 40.2 | 29.3 | 30.5 |
| 60 | 40.1 | 29.2 | 30.7 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.23: Reaction temperature (64$^0$C)**

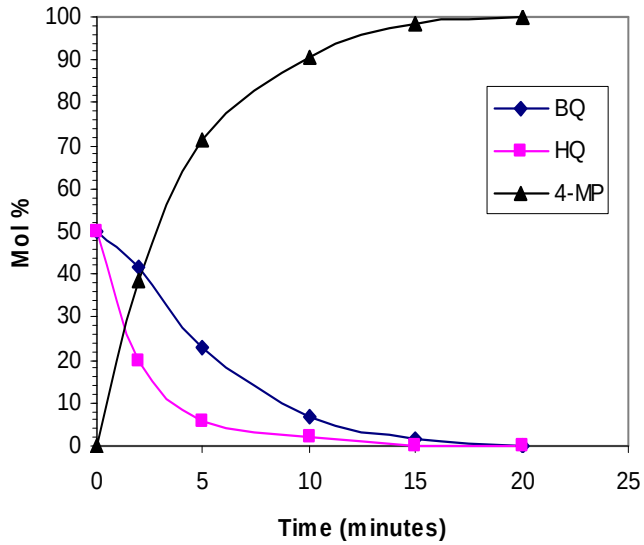



**Figure 2.24: Reaction temperature (50$^0$C)**

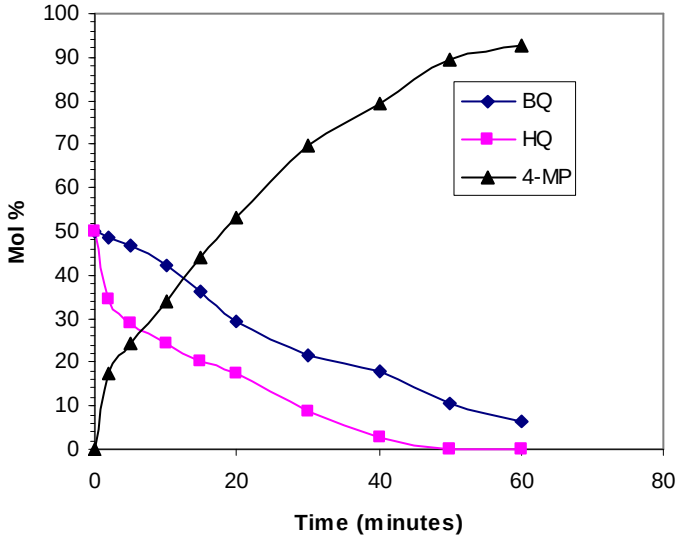



**Figure 2.25: Reaction temperature (30$^0$C)**

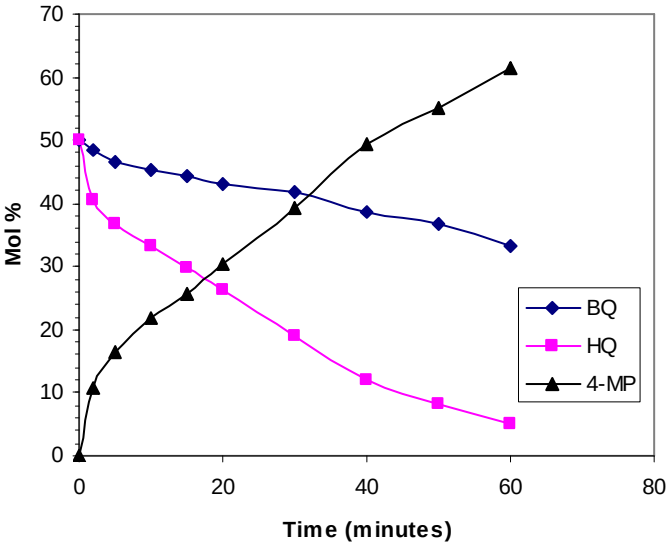
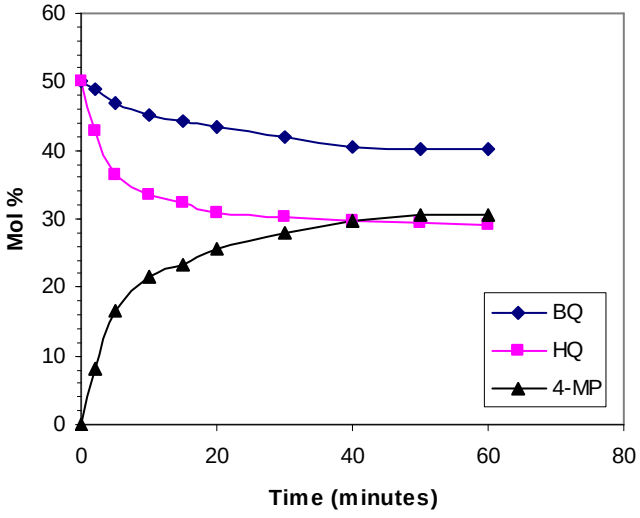



**Figure 2.26: Reaction temperature (room temperature)**




The results depicted above show a rapid decrease in the rate of reaction with decreasing reaction temperature. As in the case of the previous set of experiments, the rate of hydroquinone consumption is significantly higher than the rate of

benzoquinone consumption. Also, the ratio of 4-methoxyphenol/benzoquinone > 2 which implies that more than one equivalent of hydroquinone is consumed for every benzoquinone consumed.

### 2.3.3 Hydroquinone:benzoquinone: Effect of acid concentration

In order to investigate the effect of increasing amounts of acid catalyst on the rate and extent of formation of 4-methoxyphenol during the reaction of hydroquinone/benzoquinone mixtures with methanol at reflux temperature (64 $^0$C), several experiments were carried out in which the amount of acid catalyst were varied from 0.051g to 0.357g. During these reactions the hydroquinone:benzoquinone mol ratio was kept constant at about 1:1 (0.9:0.9mmol). The amount of acid [conc. $H_2SO_4$ (18M)] was increased from 0.051g (0.519mmol) to 0.102g (1.038mmol), to 0.153g (1.557mmol), to 0.255g (2.595mmol) and finally to 0.357g (3.633mmol). The amount of methanol (20 mL) was kept constant in all the reactions. The results of these reactions are summarized in Tables 2.22 – 2.26, and illustrated graphically in Figures 2.27 – 2.31.

**Table 2.22: Concentration of acid catalyst= 0.051g (0.519mmol)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50.0 | 50.0 | 0 |
| 2 | 41.8 | 19.8 | 38.3 |
| 5 | 23.1 | 5.5 | 71.4 |
| 10 | 7.0 | 2.2 | 90.9 |
| 15 | 1.3 | 0 | 98.7 |
| 20 | 0 | 0 | 100 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.23: Concentration of acid catalyst= 0.102g (1.038mmol)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 41.5 | 4.5 | 54.0 |
| 5 | 13.5 | 0 | 86.5 |
| 10 | 3.4 | 0 | 96.6 |
| 15 | 3.0 | 0 | 97.0 |
| 20 | 1.2 | 0 | 98.8 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.24: Concentration of acid catalyst= 0.153g (1.557mmol)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 26.1 | 1.6 | 72.3 |
| 5 | 9.8 | 0 | 90.2 |
| 10 | 4.5 | 0 | 95.5 |
| 15 | 4.6 | 0 | 95.4 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.25: Concentration of acid catalyst= 0.255g (2.595mmol)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 8.1 | 0 | 91.9 |
| 5 | 9.8 | 0 | 90.2 |
| 10 | 7.6 | 0 | 92.4 |
| 15 | 9.1 | 0 | 90.9 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.26: Concentration of acid catalyst= 0.357g (3.633mmol)**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 9.6 | 0 | 90.4 |
| 5 | 8.4 | 0 | 91.6 |
| 10 | 13.4 | 0 | 86.6 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure 2.27: Acid catalyst=0.051g**

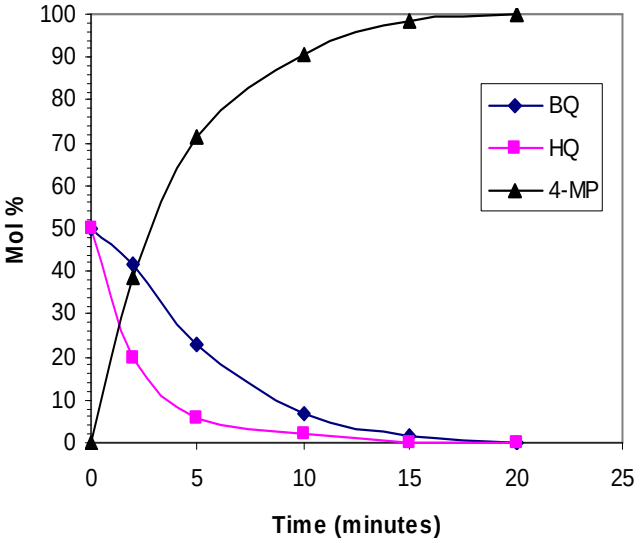



**Figure 2.28: Acid catalyst=0.102g**

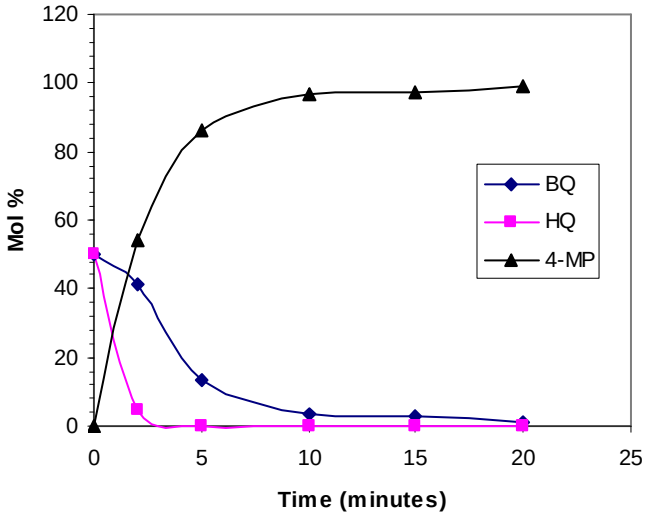



**Figure 2.29: Acid catalyst=0.153g**

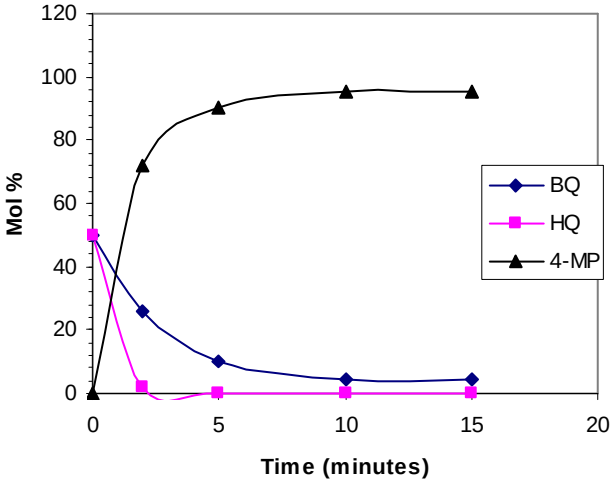



**Figure 2.30: Acid catalyst=0.255g**

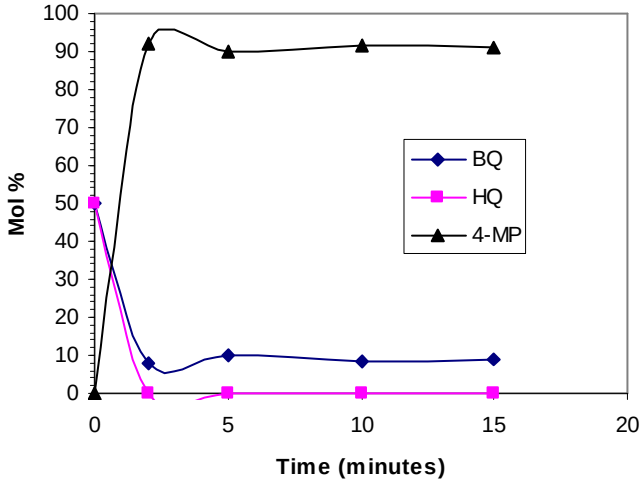
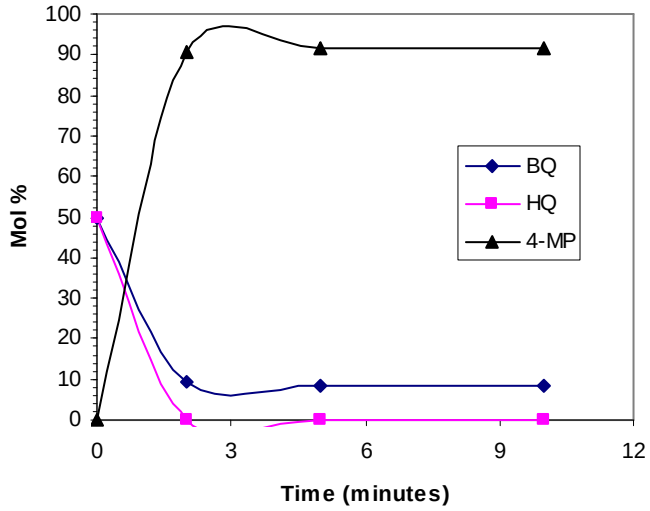


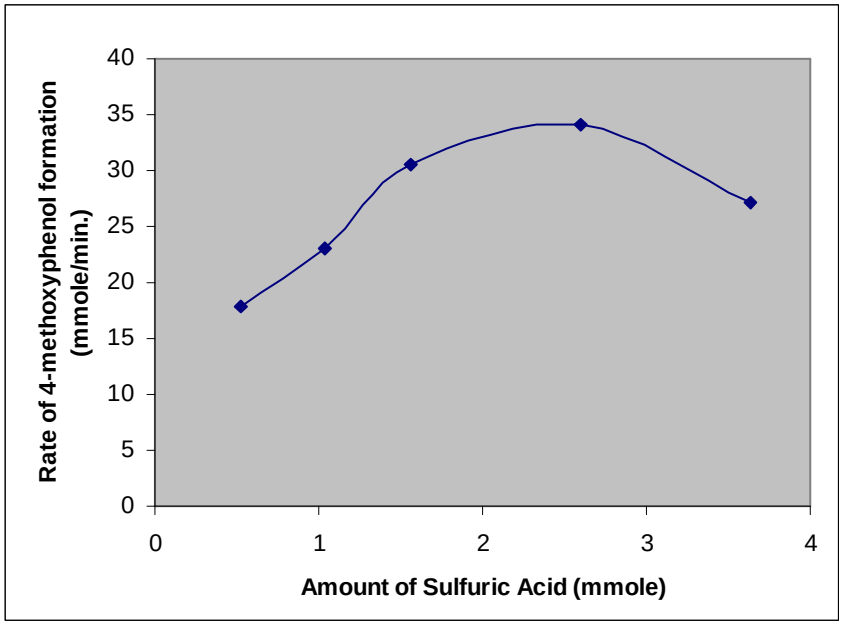
**Figure 2.31: Acid catalyst=0.357g**




Increasing the amount of acid catalyst affects the reaction in a number of ways, namely:

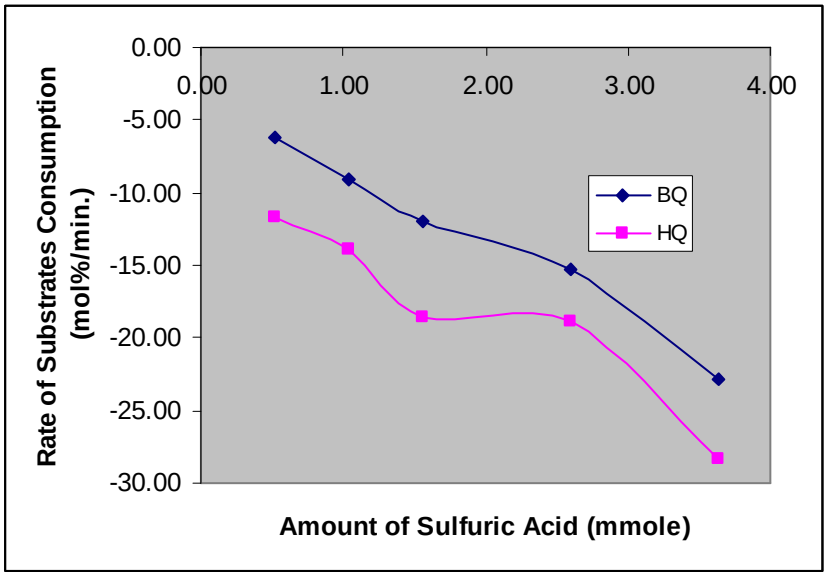
- The rate of reaction (measured as the rate of formation of 4-methoxyphenol over the first 2 minutes of the reaction) increases sharply as the acid concentration is increased (Figure 2.32).

**Figure 2.32: Rate of 4-methoxyphenol formation versus catalyst loading**



- The rates of hydroquinone and benzoquinone consumption as a function of catalyst loading show an interesting trend (Figure 2.33). Thus, as the catalyst loading is increased from about 0.5 mmol to 1.0 mmol, the rate of hydroquinone consumption more than doubles while the rate of benzoquinone consumption remains virtually unchanged. However, above a catalyst loading of 1 mmol, the rate of benzoquinone consumption increases whilst the rate of hydroquinone seems to remain virtually constant. The reason for the apparent constancy in hydroquinone consumption above catalyst loadings of about 1 mmol is, however, due to the fact that the hydroquinone reacts so fast to virtually a zero concentration that further rate increases could not be measured under the reaction conditions used.

**Figure 2.33: Rates of hydroquinone and benzoquinone consumption versus catalyst loading**



### 2.3.4 Effect of acid concentration on higher hydroquinone:benzoquinone ratios

In order to observe the effect of increasing amounts of acid catalyst on the higher hydroquinone:benzoquinone ratios, two experiments were carried out in which the amount of acid catalyst [conc. $H_2SO_4$ (18M)] was kept constant 0.153g (1.557mmol). During these reactions, the hydroquinone:benzoquinone mole ratios were 5:1 (0.9:0.18mmol) and 10:1 mmol (0.9:0.09mmol). The amount of methanol (20 mL) and the reaction temperature of $64^0$C were kept constant in both the reactions. The results of these reactions are summarized in Tables 2.27 – 2.28, and illustrated graphically in Figures 2.34 – 2.35.

**Table 2.27: HQ:BQ, ratio = 5:1, acid=0.153g**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 16.6 | 83.3 | 0 |
| 2 | 2.5 | 32.2 | 65.2 |
| 5 | 2.1 | 9.1 | 88.7 |
| 10 | 1.8 | 4.6 | 93.5 |
| 15 | 1.6 | 0.0 | 98.3 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Table 2.28: HQ:BQ, ratio = 10:1, acid=0.153g**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 9.0 | 90.9 | 0 |
| 2 | 2.1 | 36.0 | 61.8 |
| 5 | 1.7 | 32.8 | 65.4 |
| 10 | 1.2 | 30.7 | 68.0 |
| 15 | 0.8 | 25.1 | 74.0 |
| 20 | 0.6 | 16.8 | 82.5 |
| 30 | 0.5 | 13.3 | 86.1 |
| 60 | 0.3 | 12.2 | 87.4 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-MP= 4-methoxyphenol

**Figure-2.34: HQ:BQ, ratio = 5:1 (acid=0.153g)**

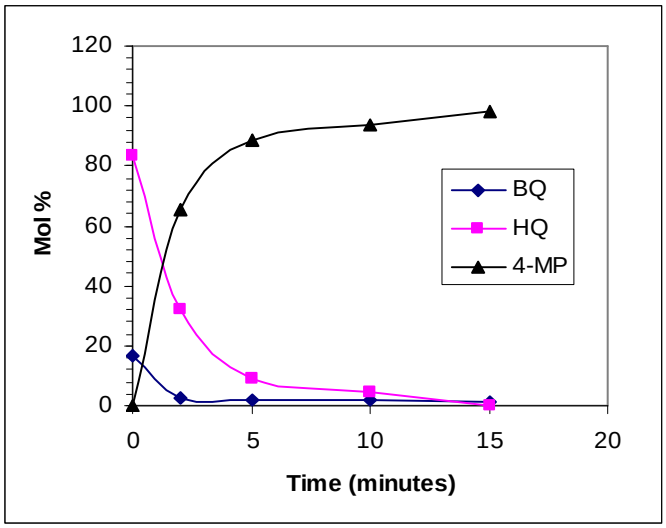
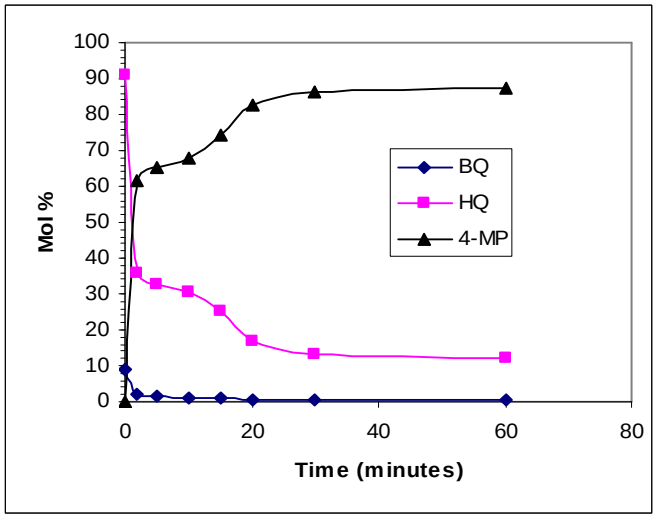



**Figure-2.35: HQ:BQ, ratio = 10:1 (acid=0.153g)**




The effect of increasing the amount of acid catalyst in the above reactions is to increase both the rate of reaction, as well as the extent of reaction as compared to reactions in which less acid catalyst is used. Thus, when using three times less sulphuric acid (Table 2.17), only 33.7% of 4-methoxyphenol product is formed compared to 87.4% when using the higher amount. In addition, the ratio 4-alkoxyphenol/benzoquinone increases from 3.97 to 5.90 for a 5:1 ratio of hydroquinone:benzoquinone and from 4.51 to 10.49 for a 10:1 hydroquinone:benzoquinone ratio.

It is also of interest to note that the ratio in which product 4-alkoxyphenol is formed to the amount of acid catalyst also decreases sharply as the hydroquinone:benzoquinone ratio is increased, irrespective of the amount of acid catalyst initially added (Table 2.29).

**Table 2.29: Effect of the amount of acid on the mole ratio (4-MP/$H_2SO_4$)**

| Mol ratio (HQ:BQ) | Amount of $H_2SO_4$ (mmol) | Mol ratio (4-MP/$H_2SO_4$) |
|---|---|---|
| 1:1 | 0.519 | 3.47 |
| 2:1 | 0.519 | 2.46 |
| 5:1 | 0.519 | 1.32 |
| 5:1 | 1.557 | 0.68 |
| 10:1 | 0.519 | 0.74 |
| 10:1 | 1.557 | 0.56 |

### 2.3.5 Nature of the alcohol

In this part of the study the use of different alcohols, namely ethanol, n-butanol, and benzyl alcohol, were investigated for their propensity to form alkoxyphenol ethers by reaction with hydroquinone/benzoquinone mixtures in the presence of sulphuric acid as the acid catalyst. These experiments were carried out by reacting the alcohol at the reflux temperature of the respective alcohol with hydroquinone:benzoquinone mixtures (mole ratio 1:1). The amount of acid catalyst (0.051g; 0.519 mmol) and the amount of alcohol (20mL) were kept constant during these reactions. The results of these reactions are summarized in Tables 2.30 – 2.32, and illustrated graphically in Figures 2.36 – 2.38.

**Table 2.30: Reaction with ethanol**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-EP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 45.3 | 17.4 | 37.3 |
| 5 | 37.9 | 7.0 | 55.1 |
| 10 | 27.1 | 3.0 | 70.0 |
| 15 | 19.5 | 1.2 | 79.3 |
| 20 | 12.5 | 0.6 | 86.9 |
| 30 | 5.7 | 0.0 | 94.3 |
| 40 | 2.9 | 0.0 | 97.1 |
| 50 | 0.0 | 0.0 | 100.0 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-EP= 4-ethoxyphenol

**Table-2.31: Reaction with n-butanol**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-BP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 5.2 | 5.3 | 89.5 |
| 5 | 4.6 | 4.2 | 91.2 |
| 10 | 1.2 | 3.1 | 95.7 |
| 15 | 1.0 | 3.3 | 95.7 |
| 20 | 1.3 | 2.9 | 95.8 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-BP= 4-butoxyphenol

**Table-2.32: Reaction with benzyl alcohol**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-BnP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 46.3 | 12.6 | 41.1 |
| 5 | 15.5 | 2.1 | 82.4 |
| 10 | 0.1 | 1.7 | 98.3 |
| 20 | 0.0 | 1.2 | 98.7 |
| 30 | 0.1 | 0.8 | 99.2 |
| 60 | 0.0 | 0.5 | 99.5 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-BnP= 4-benzyloxyphenol

**Figure 2.36: Reaction with ethanol**

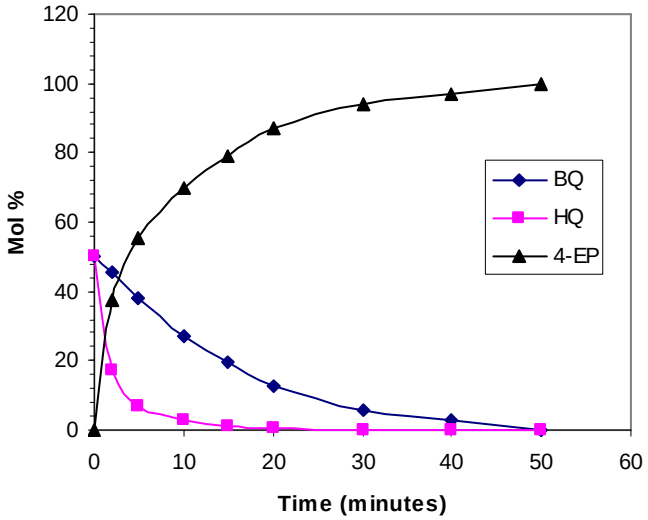



**Figure 2.37: Reaction with n-butanol**

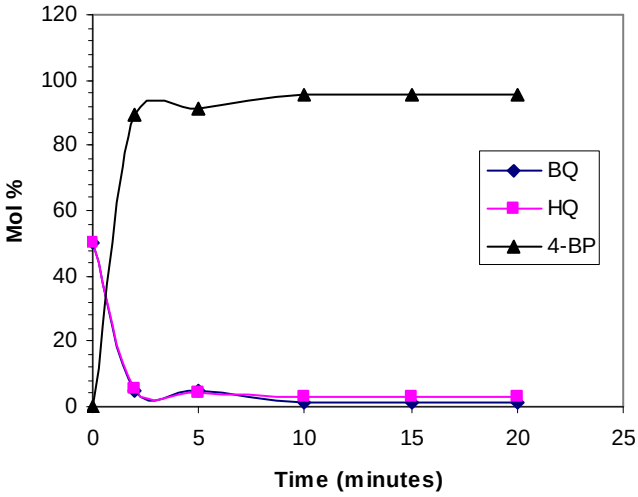
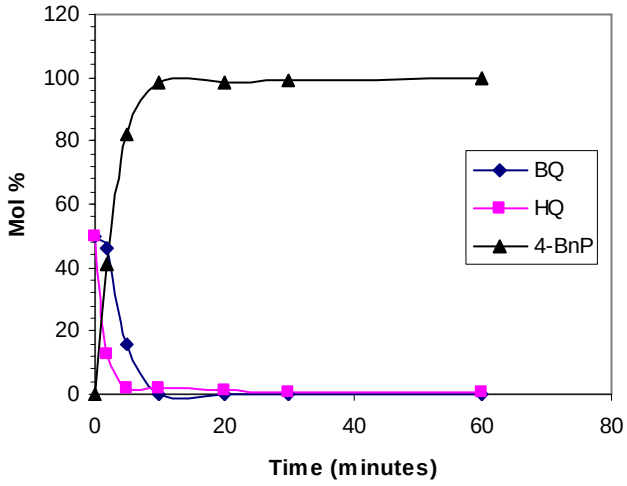



**Figure 2.38: Reaction with benzyl alcohol**



### 2.3.6 Reaction of different alcohols at constant reaction conditions

The reactivity of different alcohols namely ethanol, n-butanol, and benzyl alcohol was investigated at constant temperature ($60^0$C). During these reactions hydroquinone:benzoquinone mole ratio 1:1, acid catalyst (0.051g; 0.519 mmol) and the amount of alcohol (20mL) were kept constant. The results of these reactions are summarized in Tables 2.33 – 2.35, and illustrated graphically in Figures 2.39 – 2.41.

**Table 2.33: Reaction with ethanol at $60^0$C**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-EP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 42.0 | 23.9 | 34.1 |
| 5 | 38.6 | 21.8 | 39.6 |
| 10 | 37.2 | 17.0 | 45.8 |
| 20 | 35.7 | 13.2 | 51.1 |
| 30 | 33.6 | 7.2 | 59.2 |
| 60 | 24.0 | 2.5 | 73.5 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-EP= 4-ethoxyphenol

**Table 2.34: Reaction with n-butanol at $60^0$C**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-BP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 48.1 | 33.7 | 18.2 |
| 5 | 47.4 | 27.0 | 25.6 |
| 10 | 46.1 | 22.3 | 31.6 |
| 20 | 41.0 | 15.6 | 43.4 |
| 30 | 37.0 | 12.1 | 50.9 |
| 60 | 30.1 | 8.7 | 61.2 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-BP= 4-butoxyphenol

**Table 2.35: Reaction with benzyl alcohol at 60$^0$C**

| Time (minutes) | BQ* (Mol %) | HQ** (Mol %) | 4-BnP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 50 | 0 |
| 2 | 41.9 | 20.6 | 37.5 |
| 5 | 23.5 | 11.1 | 65.4 |
| 10 | 12.3 | 2.2 | 85.5 |
| 20 | 6.2 | 1.7 | 92.1 |
| 30 | 3.5 | 0.9 | 95.6 |
| 60 | 3.2 | 0 | 96.8 |

*BQ= benzoquinone; **HQ= hydroquinone; ***4-BnP= 4-benzyloxyphenol

**Figure 2.39: Reaction with ethanol at 60$^0$C**

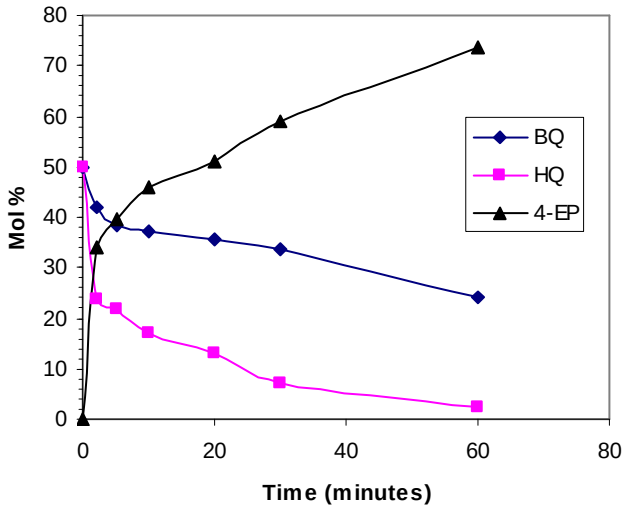



**Figure 2.40: Reaction with n-butanol at 60$^0$C**

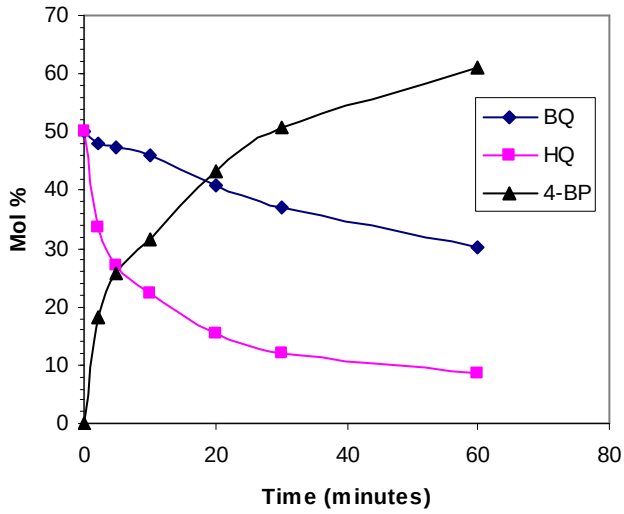
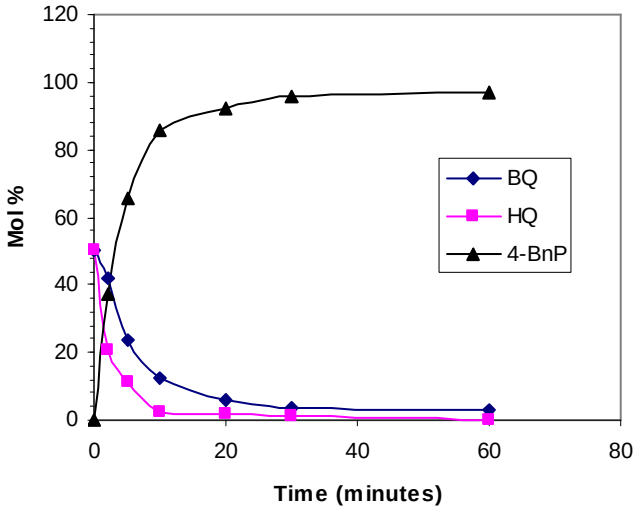



**Figure 2.41: Reaction with benzyl alcohol at 60$^0$C**



The results obtained show that other alcohols are also effective in forming alkoxy-substituted phenols by reaction of the respective alcohol with a mixture of hydroquinone and benzoquinone in the presence of an acid catalyst. These reactions show similar behaviour to that observed for the reaction of methanol with a 1:1 mixture of hydroquinone and benzoquinone, namely:

- Near quantitative yields of the desired mono-substituted alkoxy-phenol; and
- A much faster rate of hydroquinone consumption compared to the rate of benzoquinone consumption.

The apparent increase in reaction rate in going from ethanol to n-butanol is probably the result of the increase in reaction temperature in going from the boiling point of ethanol (78$^{o}$C) to the boiling point of n-butanol (116$^{o}$C), and not as a result of a faster rate of attack by n-butanol. In fact, at lower reaction temperatures, the reaction of n-butanol is somewhat slower than observed for ethanol (cf. Tables 2.30 and 2.31 with Tables 2.33 and 2.34). However, the reactivity of benzyl alcohol is clearly higher than the linear alcohols as may be expected on the basis of higher reactivity of benzylic alcohols in nucleophilic substitution reactions.

### 2.3.7 Hydroquinone:benzoquinone: Cross-over reactions with substituted hydroquinone/benzoquinone

In an attempt to gain further information regarding the course of the reaction when an alcohol is reacted with a mixture of hydroquinone and benzoquinone in the presence of an acid catalyst, it was decided to carry out several cross-over reactions in which hydroquinone is reacted with 2-*tert*-butylbenzoquinone and also where 2-*tert*-butylhydroquinone is reacted with benzoquinone in the presence of methanol and acid catalyst. In the first of these reactions, 0.91mmol (0.151g) of 2-*tert*-butylhydroquinone and 0.91mmol (0.0984g) of benzoquinone was reacted with methanol (20mL) to which 0.051g (0.519mmol) of concentrated $H_2SO_4$ (18M) was added. Aliquots of the reaction mixture were removed from the reaction vessel and analyzed by means of GC-MS. Figure 2.42 depicts the GC-MS chromatogram obtained for the reaction mixture after a reaction time of 2 minutes, while Figure

2.43 depicts the chromatogram obtained for the reaction mixture after a reaction time of 60 minutes. The identities of the peaks numbered 1 – 9 in Figures 2.42 and 2.43 have been assigned on the basis of their respective mass fragmentation patterns as shown in Figures 2.44 – 2.53.

**Figure 2.42: GC-MS chromatogram (2-*t*-butylhydroquinone reaction): Reaction time = 2 minutes**

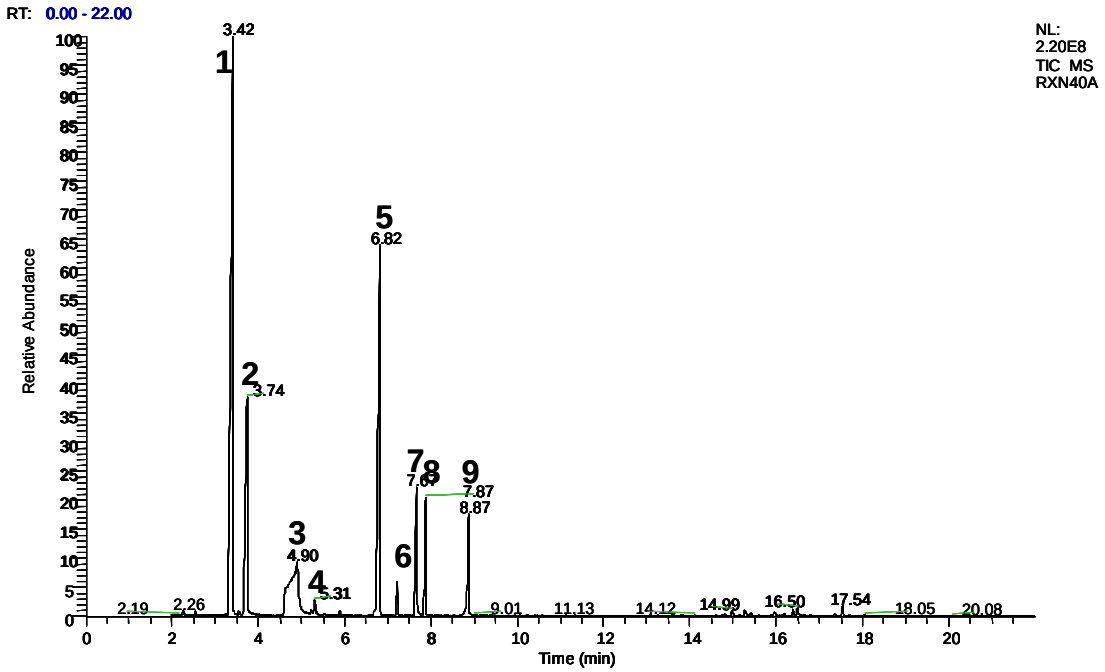



**Figure 2.43: GC-MS chromatogram (2-*t*-butylhydroquinone reaction): Reaction time = 60 minutes**

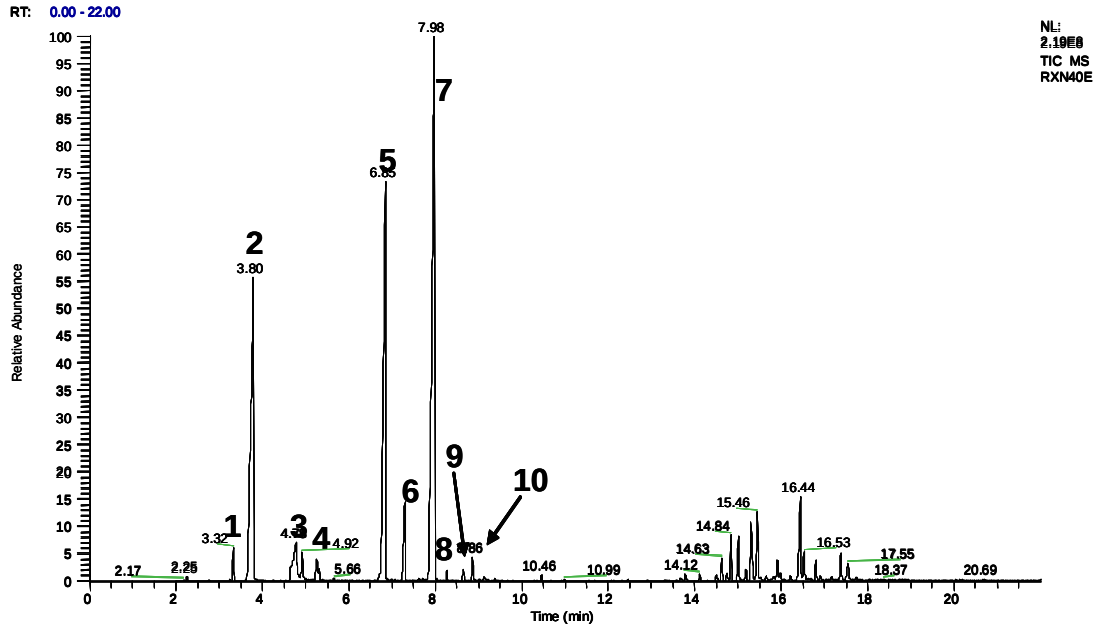
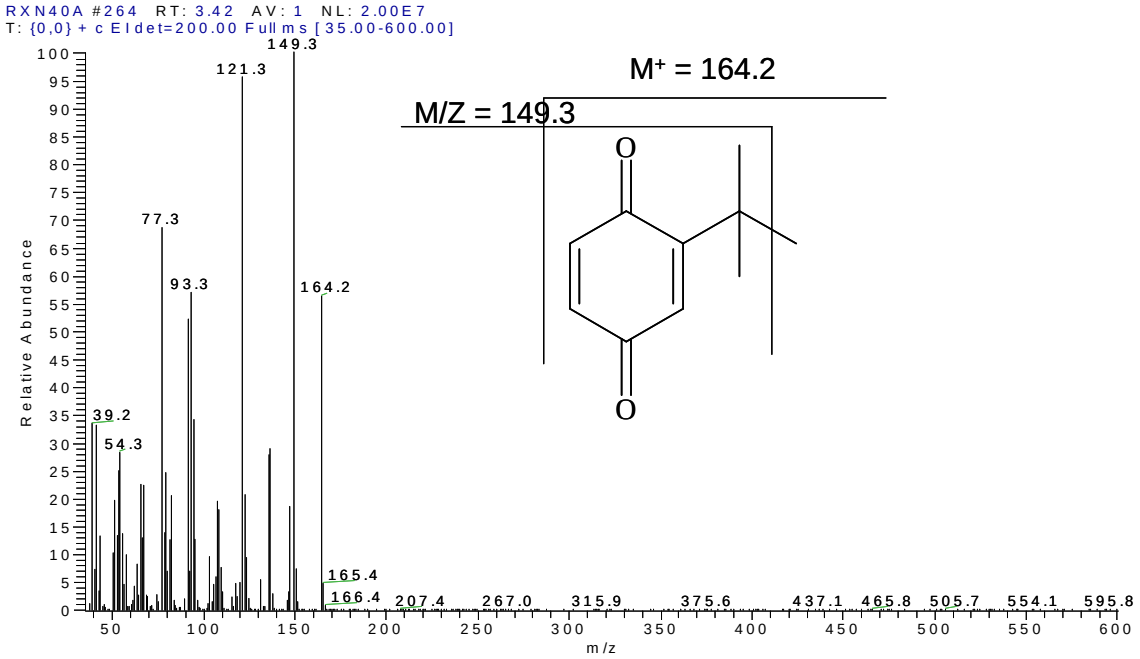
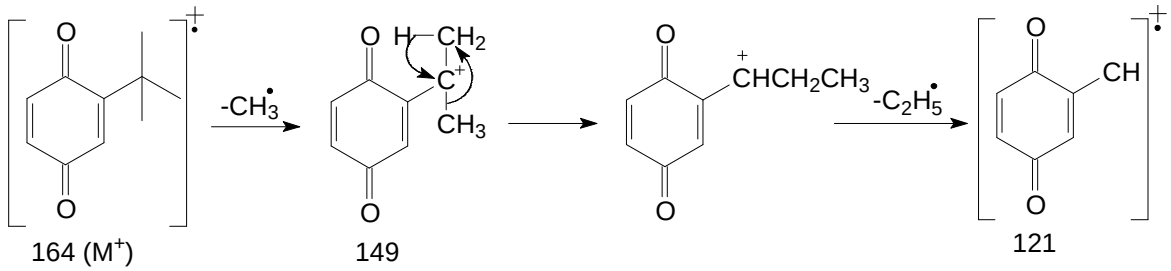


**Figure 2.44: Mass fragmentation pattern: Peak No. 1**




The secondary fragmentation of the initially formed M/Z 149 of *tert*-butylbenzoquinone may be illustrated as shown below in Scheme 24.




**Scheme-24: Mass fragmentation pattern of *tert*-butylbenzoquinone**

**Figure 2.45: Mass fragmentation pattern: Peak No. 2**

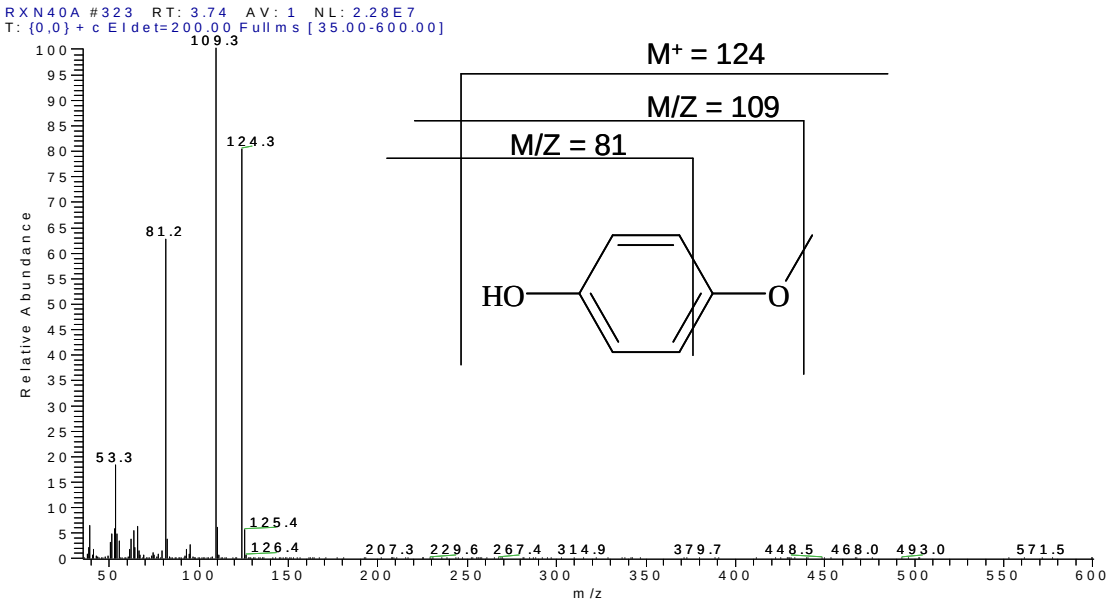



**Figure 2.46: Mass fragmentation pattern: Peak No. 3**

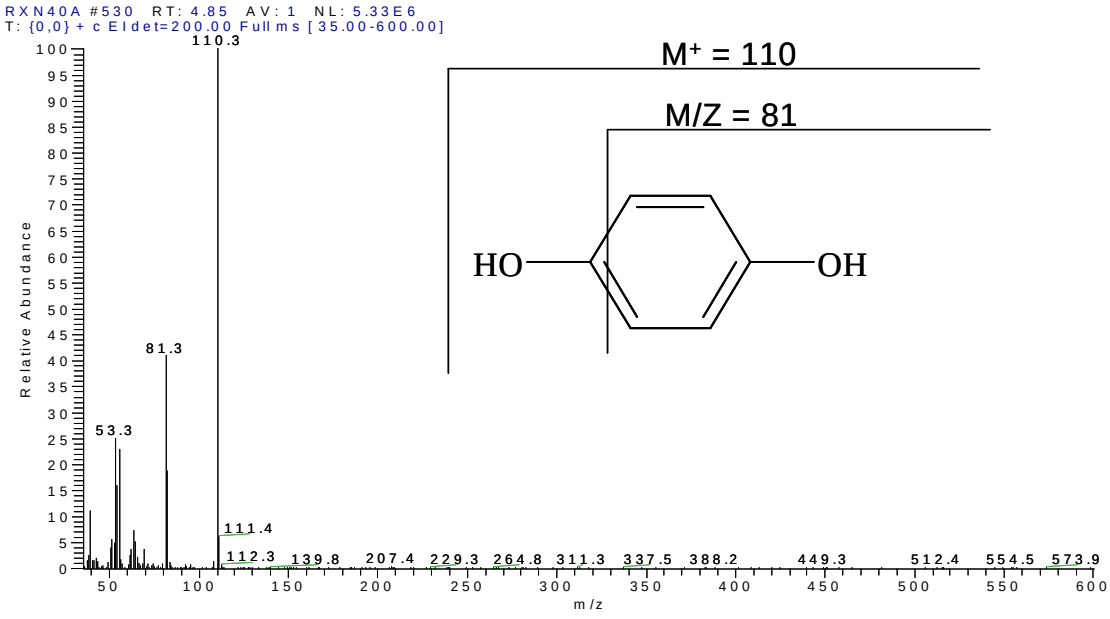


**Figure 2.47: Mass fragmentation pattern: Peak No. 4**

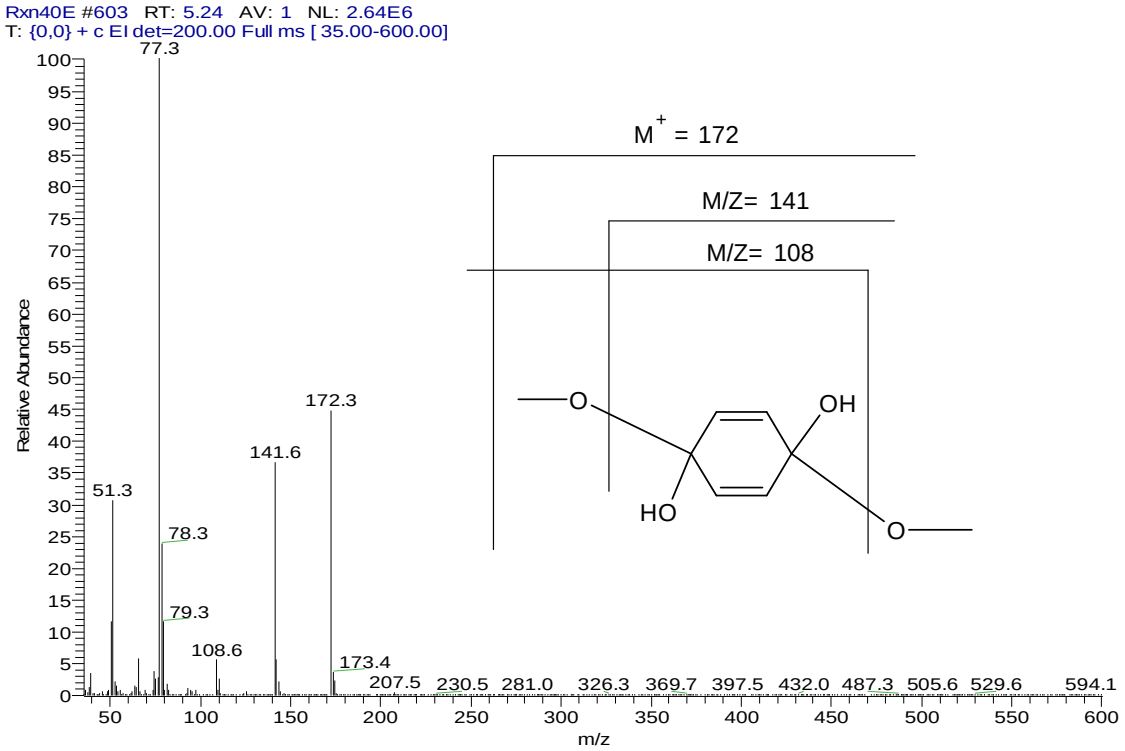



**Figure 2.48: Mass fragmentation pattern: Peak No. 5**

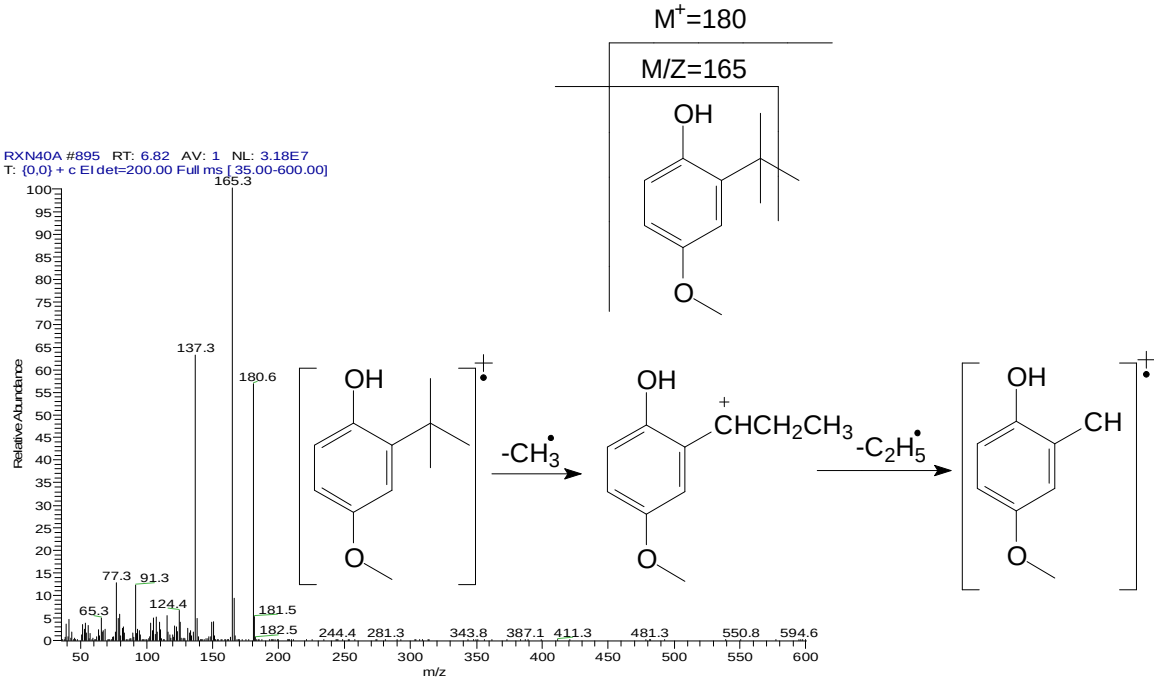


**Figure 2.49: Mass fragmentation pattern: Peak No. 6**

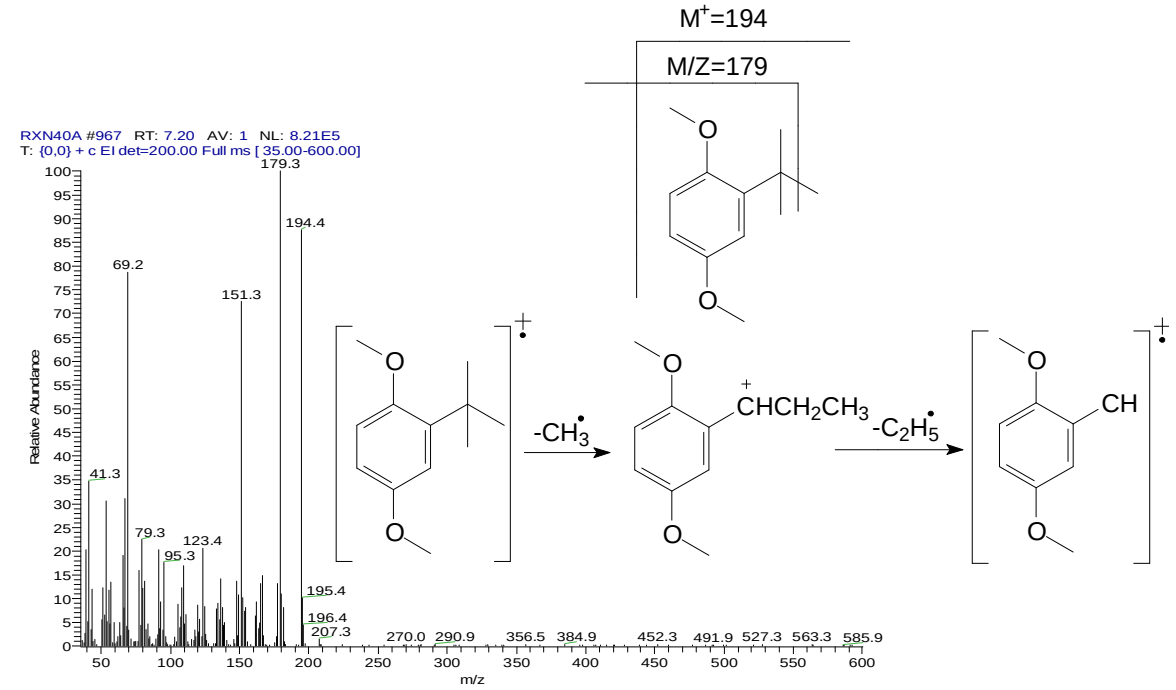



**Figure 2.50: Mass fragmentation pattern: Peak No. 7**

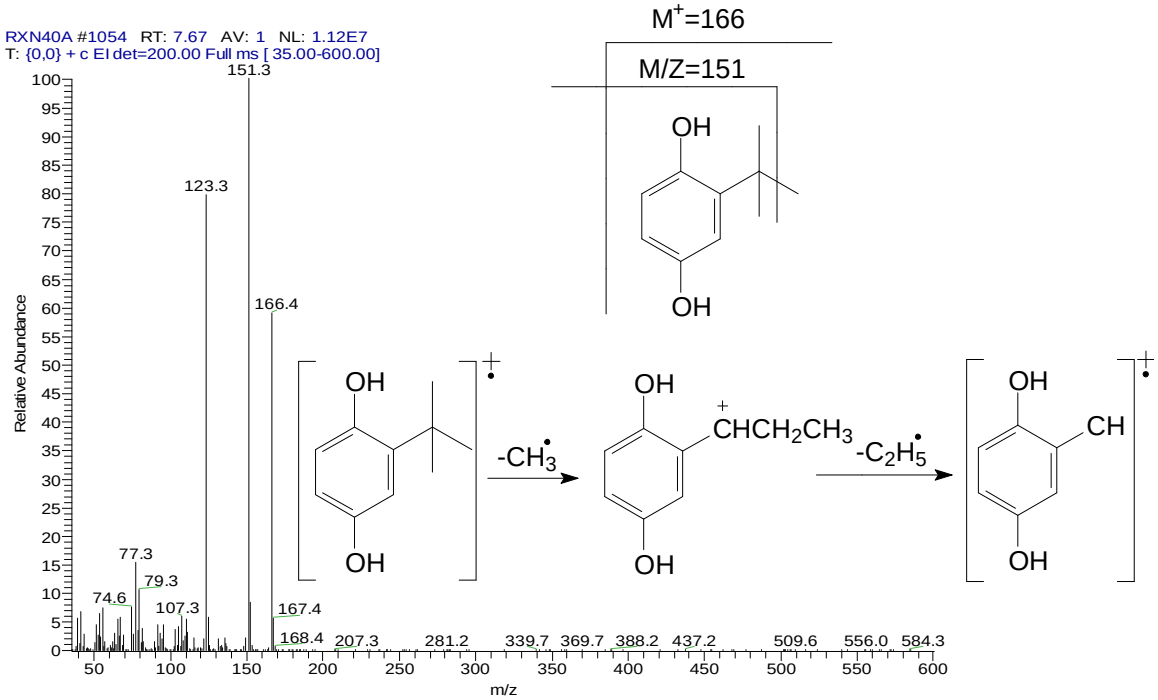


**Figure 2.51: Mass fragmentation pattern: Peak No. 8**

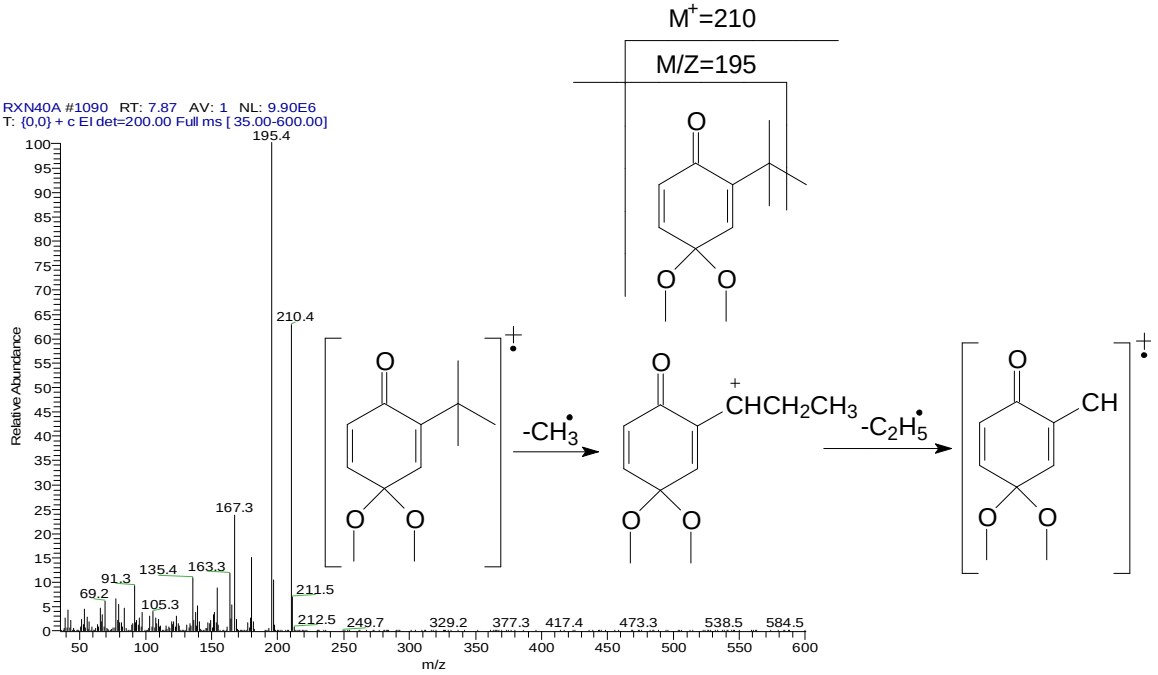



**Figure 2.52: Mass fragmentation pattern: Peak No. 9**

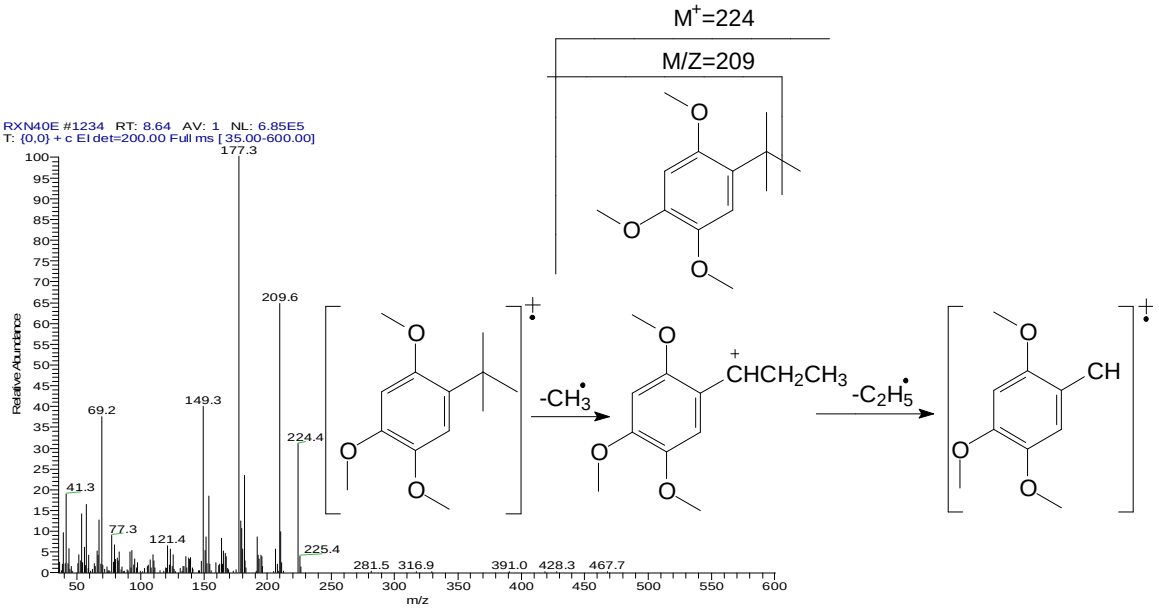
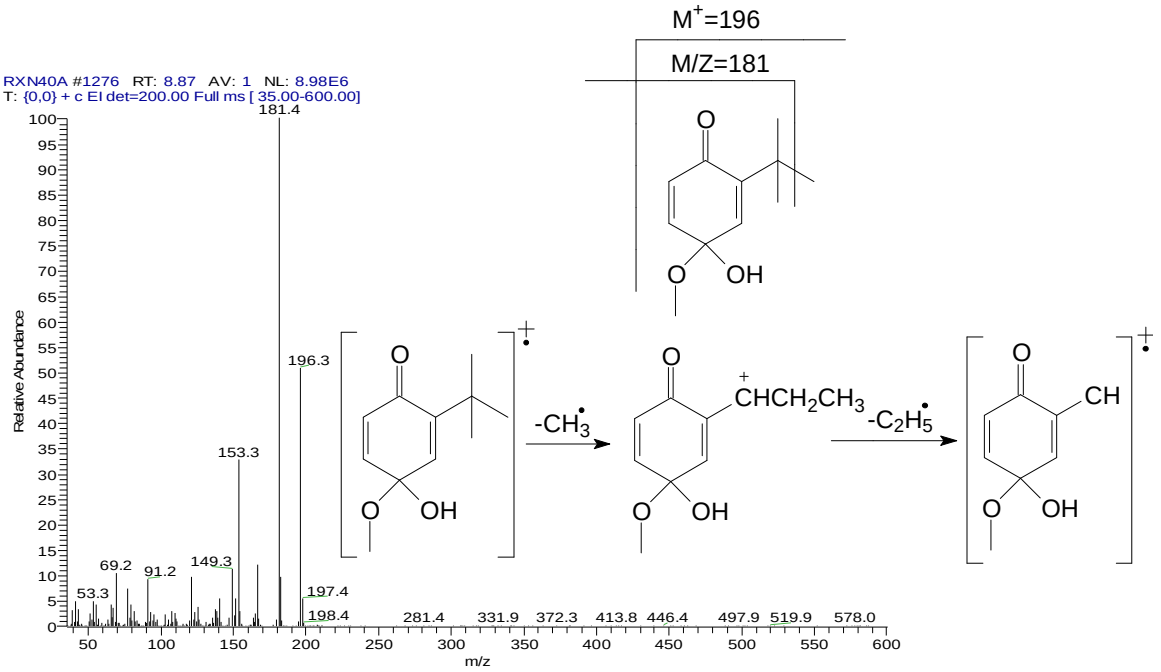


**Figure 2.53: Mass fragmentation pattern: Peak No. 10**




In the second of these cross-over reactions, 0.90mmol (0.15g) of 2-*tert*-butylbenzoquinone and 0.90mmol (0.1g) of hydroquinone was reacted with methanol (20mL) to which 0.051g (0.519mmol) of concentrated $H_2SO_4$ (18M) was added. Aliquots of the reaction mixture were removed from the reaction vessel as before and analyzed by means of GC-MS. Figure 2.54 depicts the GC-MS chromatogram obtained for the reaction mixture after a reaction time of 2 minutes, while Figure 2.55 depicts the chromatogram obtained for the reaction mixture after a reaction time of 60 minutes.

**Figure 2.54: GC-MS chromatogram (2-*t*-butylbenzoquinone reaction):**

**Reaction time = 2 minutes**

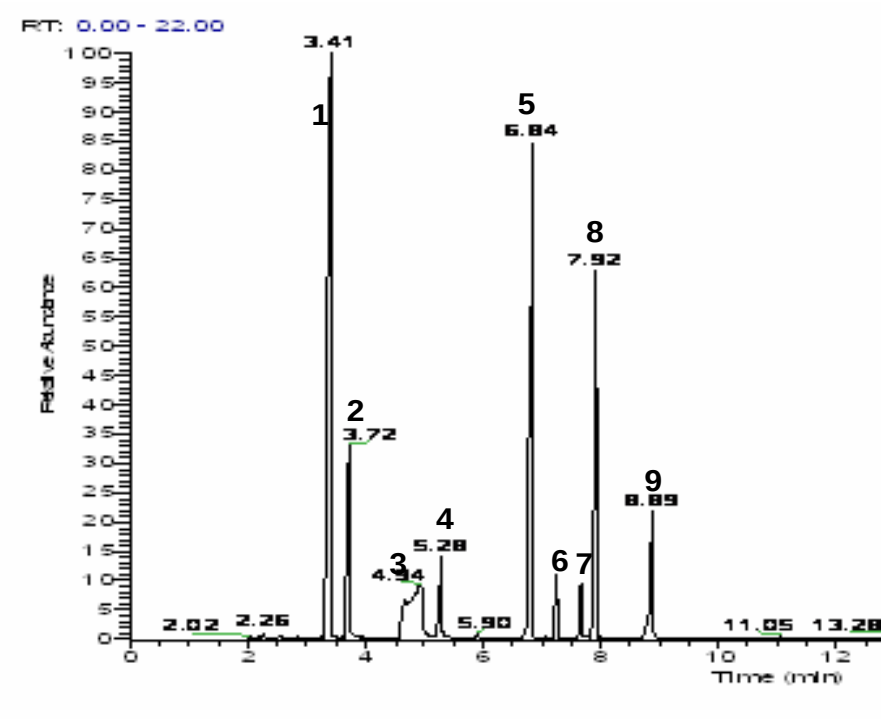
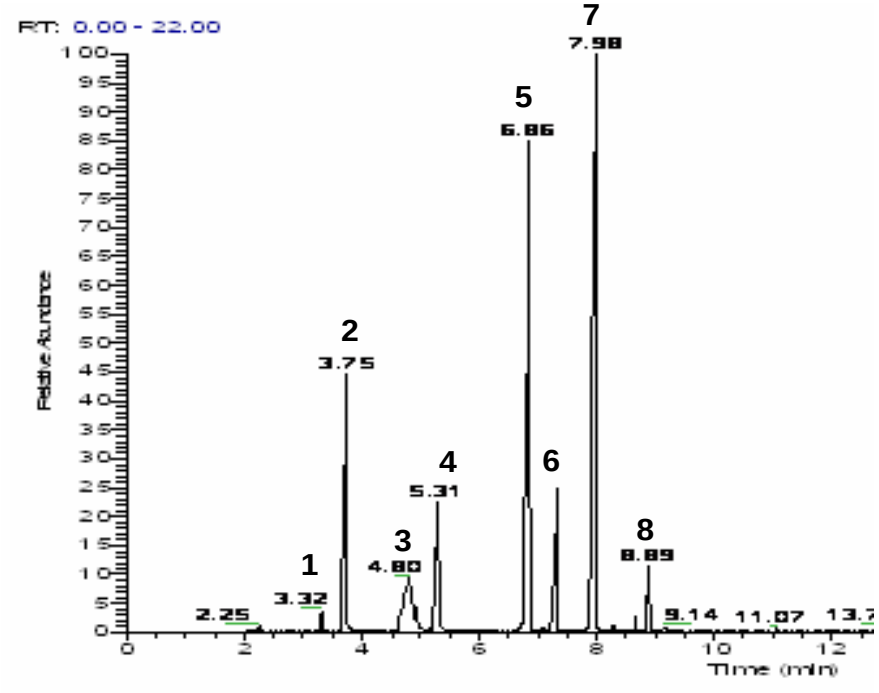



**Figure 2.55: GC-MS chromatogram (2-*t*-butylbenzoquinone reaction):**

**Reaction time = 60 minutes**



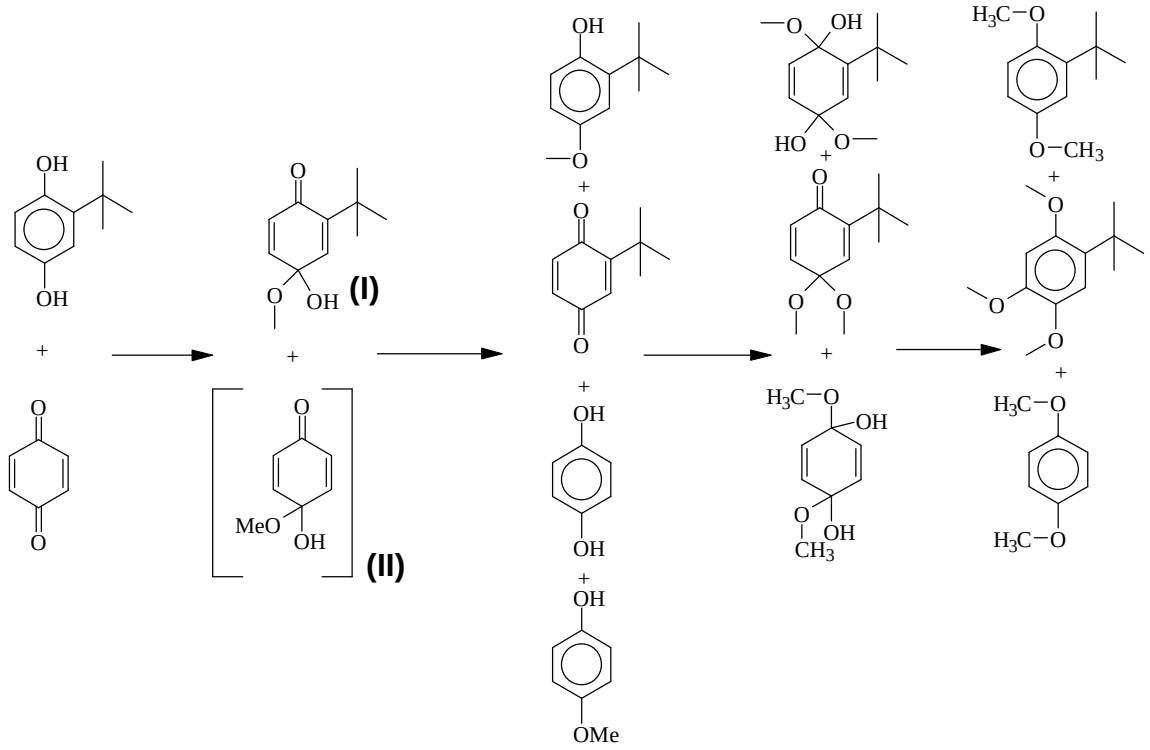
The peaks numbered 1 – 8 in Figures 2.42 and 2.43 have the same assignments as the corresponding peaks 1 – 8 in Figures 2.54 and 2.55.

### 2.3.8 Discussion: Reaction of hydroquinone and benzoquinone mixtures with alcohols

Any explanation of the reaction mechanism at work during the reaction of an alcohol with a mixture of hydroquinone and benzoquinone needs to explain a number of observations, including:

- The observation that no reaction occurs when hydroquinone or benzoquinone alone is reacted with an alcohol alone in the presence of an acid catalyst;
- The observation that no reaction occurs in the absence of acid catalyst;
- The observation that hydroquinone is consumed much faster than benzoquinone during these reactions and
- The formation of intermediate products observed during the cross-over reactions.

Based on the results of the cross-over reactions, the following reaction scheme may be proposed to explain the progress of the reaction of 2-*tert*-butylhydroquinone and benzoquinone with methanol in the presence of sulphuric acid as acid catalyst (Scheme 25):




**Scheme-25: Proposed reaction scheme: 2-*t*-butylhydroquinone, benzoquinone and methanol**

As shown above, the reaction proceeds through two intermediates, 2-(*tert*-butyl)-4-hydroxy-4-methoxycyclohexa-2,5-dien-1-one **(I)** and 4-hydroxy-4-methoxycyclohexa-2,5-dien-1-one **(II)**. The latter compound is not stable enough to be observed since it re-aromatizes rapidly to form 4-methoxyphenol, and its formation is invoked on the basis of the observation of **[I]**[76] since alkyl substituents such as the *tert*-butyl group imparts sufficient stabilisation for these cyclohexadien-1-one compounds to be observed and even isolated.[77] The primary reaction products, 2-(*tert*-butyl)-4-methoxyphenol and 4-methoxyphenol are formed by elimination of water and re-aromatization from 2-(*tert*-butyl)-4-hydroxy-4-methoxycyclohexa-2,5-dien-1-one and 4-hydroxy-4-methoxycyclohexa-2,5-dien-1-one. The formation of 1,4-dimethoxybenzene and 2-(*tert*-butyl)-1,4-dimethoxybenzene can be explained in an analogous manner by eliminating water from the corresponding 1,4-dimethoxycyclohexadienol intermediates as is indicated by the observation of 1,4-dimethoxycyclohexa-2,5-dien-1,4-diol in the

GC-MS traces. It is, however, not clear from the results described thus far whether 1,4-dimethoxycyclohexa-2,5-dien-1,4-diol and 2-(*tert*-butyl)-1,4-dimethoxycyclohexa-2,5-dien-1,4-diol are formed directly from 2-(*tert*-butyl)-4-hydroxy-4-methoxycyclohexa-2,5-dien-1-one **(I)** and 4-hydroxy-4-methoxycyclohexa-2,5-dien-1-one **(II)**, respectively, or whether they are formed from the respective methoxyphenols.

In order to investigate whether 1,4-dimethoxycyclohexa-2,5-dien-1,4-diol and 2-(*tert*-butyl)-1,4-dimethoxycyclohexa-2,5-dien-1,4-diol are formed from the respective methoxycyclohexa-2,5-dien-1-one intermediates or from the respective 4-methoxyphenol, two experiments were carried out where 4-methoxyphenol was reacted separately with benzoquinone and hydroquinone. In these reactions, the benzoquinone/hydroquinone:4-methoxyphenol mole ratio was 1:1, the reaction temperature $64^0$C, the amount of acid catalyst (0.051g, 0.519 mmol), and the amount of methanol 20mL, all of which were kept constant.

The results obtained for these reactions (Tables 2.36 and 2.37) clearly show that 4-methoxyphenol does not react with methanol in the presence of either of hydroquinone or benzoquinone and sulphuric acid catalyst. This implies that the observed 1,4-dimethoxybenzene products, hence 1,4-dimethoxycyclohexa-2,5-dien-1,4-diol and 2-(*tert*-butyl)-1,4-dimethoxycyclohexa-2,5-dien-1,4-diol, are formed directly from the respective methoxycyclohexa-2,5-dien-1-one intermediates.

In the case of the *tert*-butyl-substituted hydroquinone, a second type of di-substitution results to form 2-(*tert*-butyl)-4,4-dimethoxycyclohexa-2,5-dien-1-one. This is most probably as a result of the stereochemical crowding around the $C_1$ position resulting from the bulky *tert*-butyl group on $C_2$. Credence for this proposal is that a similar compound is not observed for the unsubstituted hydroquinone.

**Table 2.36: BQ + 4-MP = 1:1 Mol**

| Time (minutes) | BQ* (Mol %) | 1,4-diMP** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 0 | 50 |
| 2 | 50 | 0 | 50 |
| 5 | 50 | 0 | 50 |
| 10 | 50 | 0 | 50 |
| 20 | 50 | 0 | 50 |
| 30 | 50 | 0 | 50 |
| 60 | 50 | 0 | 50 |

*BQ=benzoquinone; **1,4-diMP=1,4-dimethoxyphenol; ***4-MP= 4-methoxyphenol

**Table 2.37: HQ + 4-MP = 1:1 Mol**

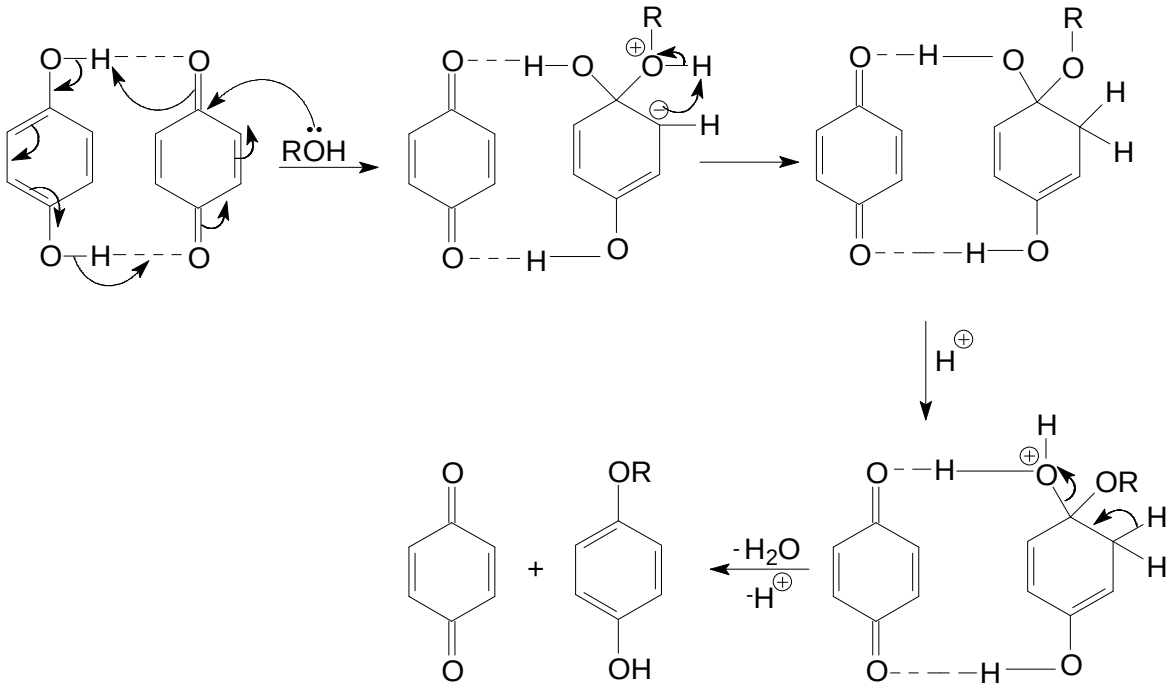
| Time (minutes) | HQ* (Mol %) | 1,4-diMP** (Mol %) | 4-MP*** (Mol %) |
|---|---|---|---|
| 0 | 50 | 0 | 50 |
| 2 | 50 | 0 | 50 |
| 5 | 50 | 0 | 50 |
| 10 | 50 | 0 | 50 |
| 20 | 50 | 0 | 50 |
| 30 | 50 | 0 | 50 |
| 60 | 50 | 0 | 50 |

*HQ=hydroquinone; **1,4-diMP=1,4-dimethoxyphenol; ***4-MP= 4-methoxyphenol

It is of interest to note that the final outcome of these cross-over reactions is the same (in terms of the appearance of the final GC-MS traces), irrespective of whether the reaction is started with 2-*tert*-butylhydroquinone, or 2-*tert*-butylbenzoquinone. This observation implies the conversion of hydroquinone into benzoquinone (as well as 2-*tert*-butylhydroquinone into 2-*tert*-butylbenzoquinone). This is confirmed by the actual observation of 2-*tert*-butylbenzoquinone in reactions where only the corresponding 2-*tert*-butylhydroquinone was initially present (see Figures 2.42, 2.43 and 2.44). Similarly, in the same reaction where benzoquinone was initially added, hydroquinone may be observed after only a very short reaction

period. The same observations also hold for the reaction where 2-*tert*-butylbenzoquinone and hydroquinone were the initial reagents (Figures 2.54 and 2.55).

The above observations therefore suggest some form of interaction between the hydroquinone and benzoquinone initially present in the reaction mixture. As discussed earlier (Chapter 1), such interaction is most likely as a result of the formation of a pi-complex between a hydroquinone and a benzoquinone, which may (some cases) be further stabilized by hydrogen bonding.[71] This type of bonding has previously been used to suggest a mechanism for the formation of phenolic ethers from hydroquinone – benzoquinone mixtures.[1] This mechanism is shown in Scheme 26 below for convenience.



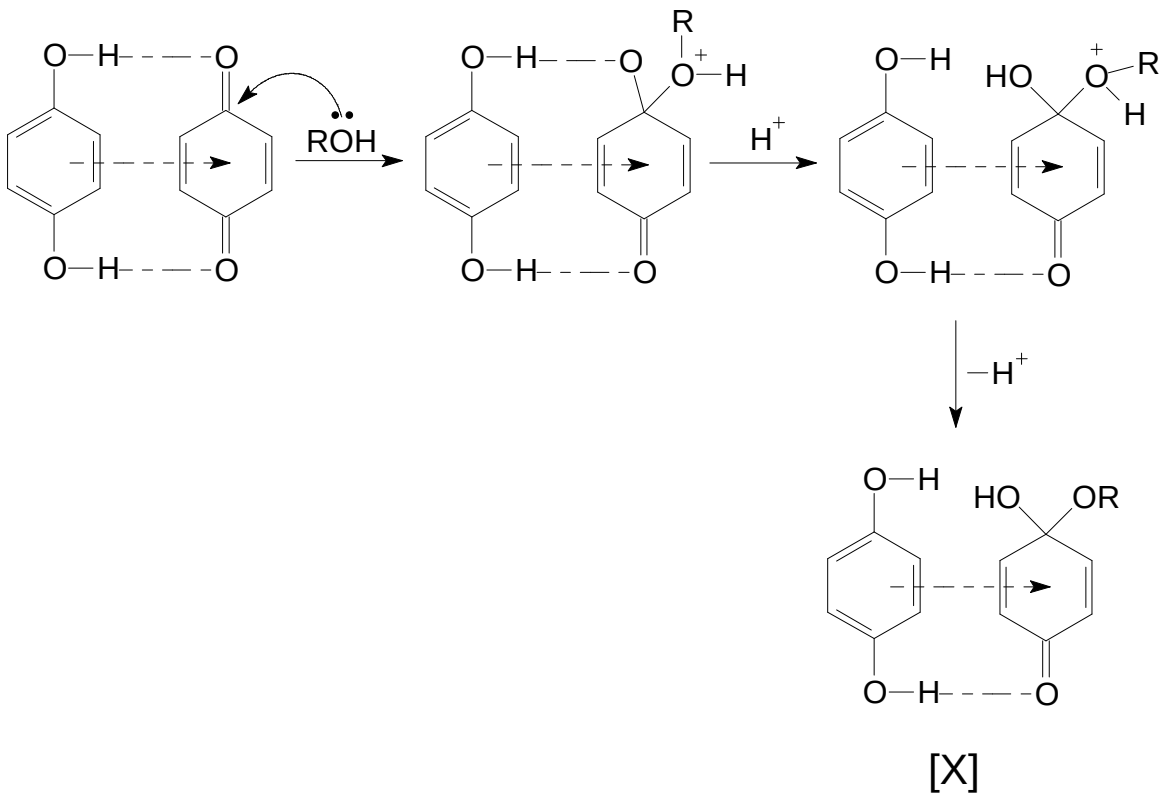

**Scheme-26: Previously proposed mechanism for the formation of phenolic ethers from a hydroquinone-benzoquinone pi-complex**

According to the above proposed mechanism, the initial step of the reaction involves the nucleophilic attack of the alcohol on the carbonyl carbon of the benzoquinone part of the complex, and the consequent formation of a cyclic

transition state in which the hydroxyl-hydrogen atoms of hydroquinone are transferred to the benzoquinone part of the complex. Following elimination of water, the phenolic ether product is formed with the synchronous oxidation of hydroquinone to benzoquinone.

A number of features of the mechanism proposed above are not consistent with the experimental observations made during the present work. The most noticeable ones are:

***The role of the acid catalyst:*** The above mechanism envisages the role of the catalyst to be only in the elimination of water from the transition state. As such, one could expect to at least observe the formation of the methylcyclohexa-2,5-dien-1-ones in the absence of catalyst if the above proposal is to be correct. Since this is never the case, one is forced to propose an alternative mechanism in which the acid catalyst must also be participating during the formation of the initial transition state and, consequently, the observed methylcyclohexa-2,5-dien-1-one intermediates. Scheme 27 envisages such an alternative role, namely the initial protonation of one of the carbonyl groups by the acid catalyst, followed by rapid attack by the alcohol nucleophile.




**Scheme-27: Initial protonation of a carbonyl group**

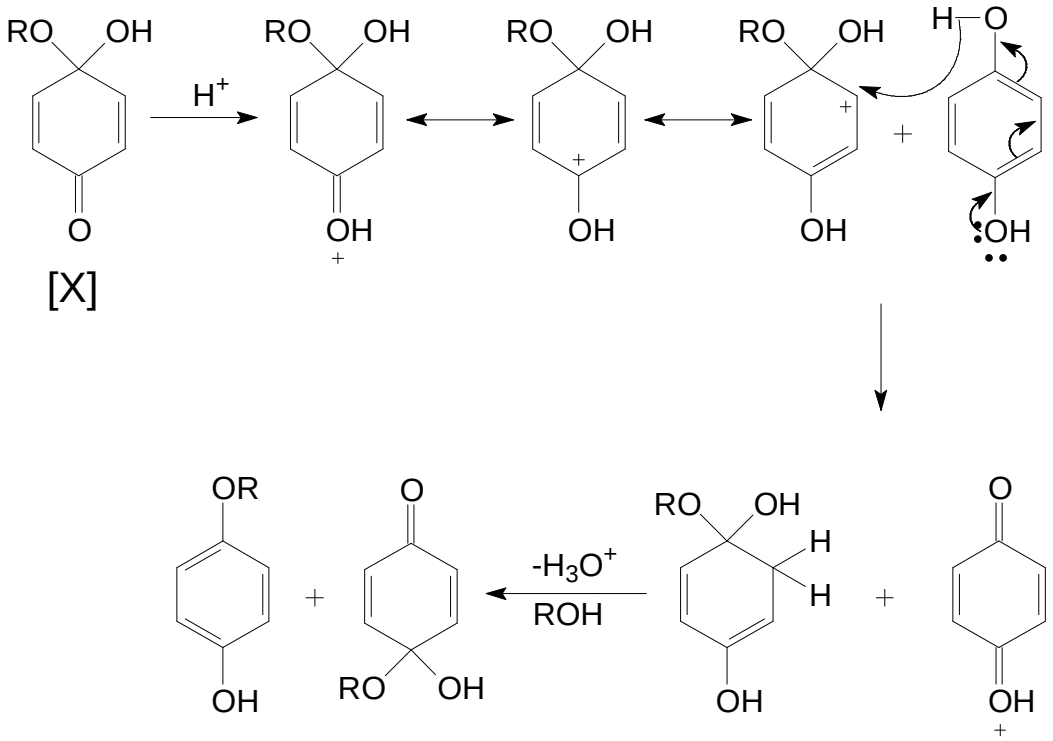
The above proposed reaction sequence probably also explains the requirement for the existence of a pi-complex between hydroquinone and benzoquinone somewhat better in terms of the stabilization of the initially protonated intermediate by means of electron transfer via the pi-bonding system of the two rings. In the absence of such a requirement, one is tempted to expect that the reaction, leading to the formation of the observed methylcyclohexa-2,5-dien-1-one intermediates at least, should proceed from benzoquinone only, even in the absence of such pi-bonding in view of the positive nature of the ring carbon atoms in benzoquinone.

***Relative rates of consumption of hydroquinone and benzoquinone:*** It was clearly shown (Section 2.3.1) during the present investigation that the initial rate of hydroquinone consumption is significantly greater than the initial rate of benzoquinone consumption. According to the mechanistic proposals in Scheme 26, the rate of benzoquinone consumption can be expected to be zero in view of

the envisaged synchronous oxidation of hydroquinone to benzoquinone for every benzoquinone molecule converted into product.

While there is little doubt regarding the synchronous oxidation of some hydroquinone to reform benzoquinone (*cf.* comparison of reaction stoichiometries – Section 2.3.1), another mechanistic route for the conversion of benzoquinone into product that does not involve the synchronous oxidation of hydroquinone must also be operating in order to explain the observed consumption of benzoquinone. Such an alternative mechanistic pathway must, however, still involve the initial formation of a pi-complex in order to "activate" the benzoquinone for reaction and to be consistent with observations that the absence of, or consumption of, either hydroquinone or benzoquinone leads to no reaction.

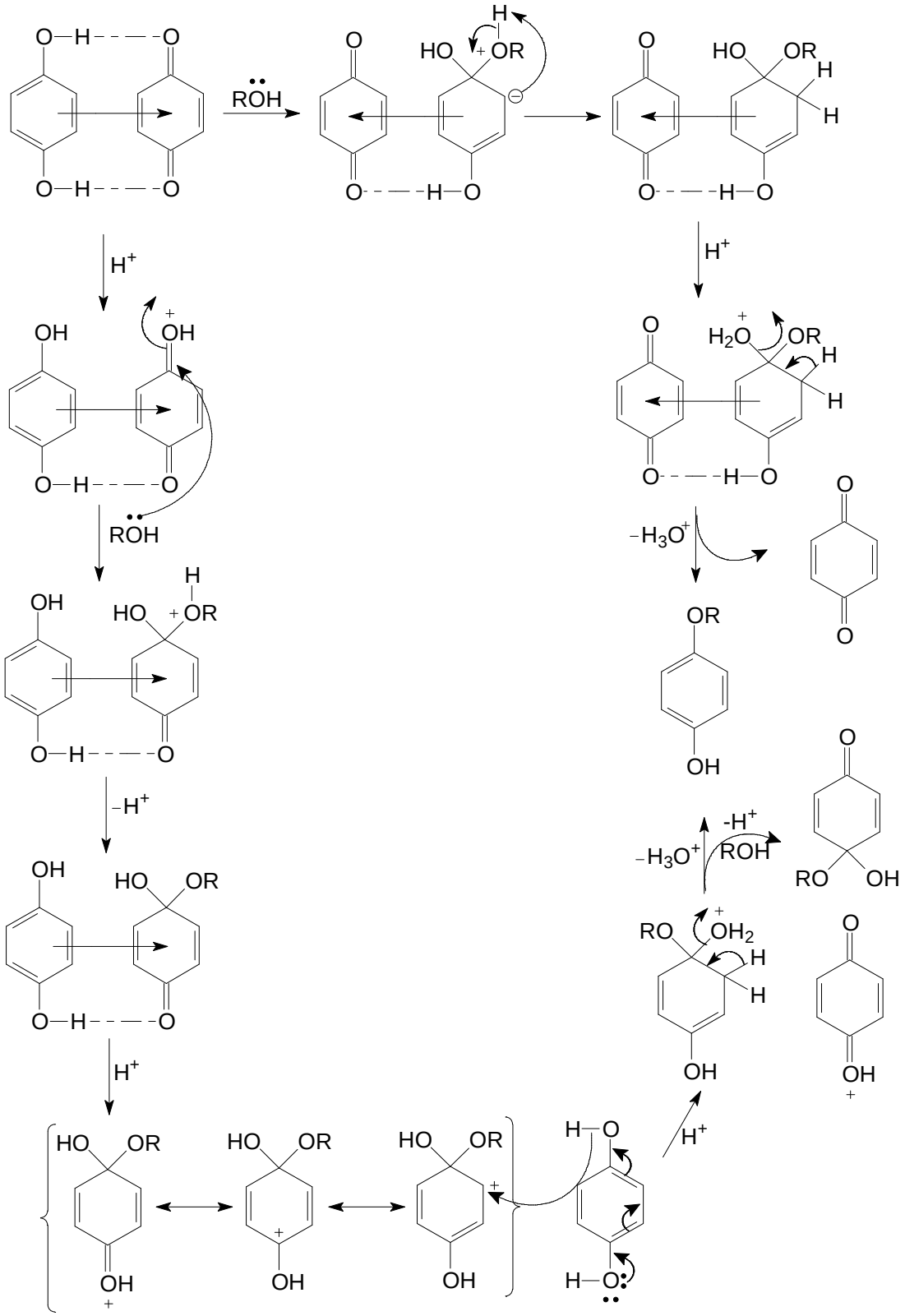
Scheme 28 below illustrates a possible pathway following the formation of intermediate [X] (Scheme 27) and is proposed to explain the consumption of benzoquinone while still resulting in the desired 4-methoxyphenol product. This pathway is closely related to the reverse process observed during aromatisation reactions where quinones (e.g. chloranil and DDQ) are used as oxidizing agents.[78]




**Scheme-28: Aromatisation of methoxycyclohexa-2,5-dien-1-one intermediates**

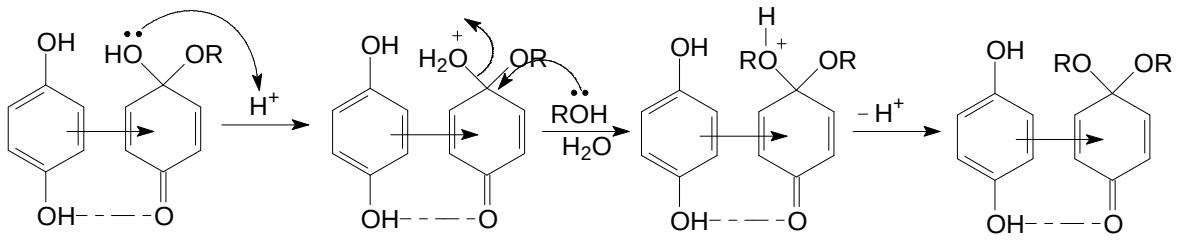
The above considerations can now be used to explain (Scheme 29) the formation of all the observed reaction products, intermediates and by-products. In addition, the mechanistic considerations depicted in Scheme 29 also explain:

- The requirement for pi-bonding between the hydroquinone and benzoquinone molecules;
- The role of the acid catalyst; and
- The relative rates of consumption of the hydroquinone and benzoquinone molecules.



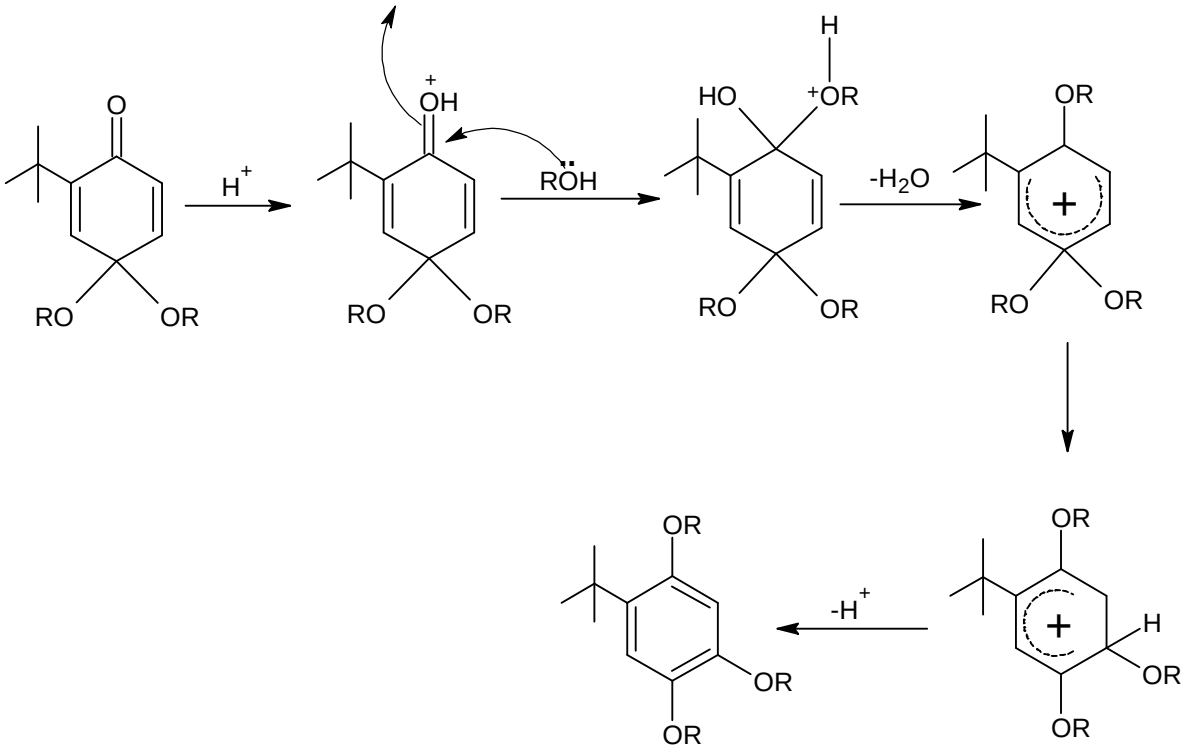
**Scheme-29: Proposed mechanism for the formation of 4-alkoxyphenols from mixtures of hydroquinones and benzoquinones**

The formation of 2-(*tert*-butyl)-4,4-dimethoxycyclohexa-2,5-dien-1-one in very small amounts during the cross-over reaction between benzoquinone and 2-*tert*-butylhydroquinone (or hydroquinone and 2-*tert*-butylbenzoquinone) may be explained as shown in Scheme 30 below.



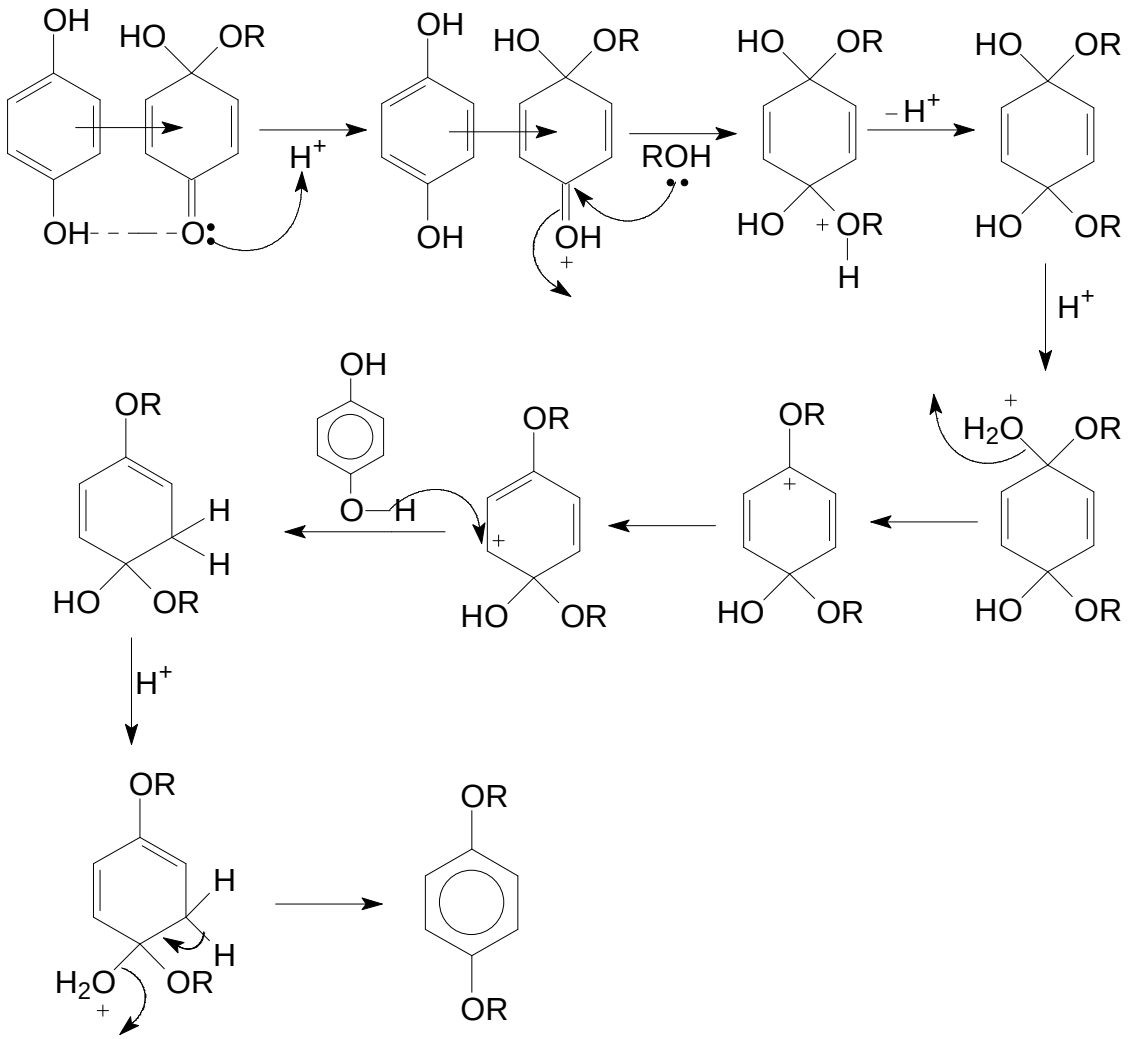

**Scheme-30: Formation of 2-(*tert*-butyl)-4,4-dimethoxycyclohexa-2,5-dien-1-one**

The presence of even smaller amounts of 5-(*tert*-butyl)-1,2,4-trimethoxybenzene in the reaction mixtures of these cross-over reactions is probably the result of the acid-catalysed dienone-phenol rearrangement of 2-(*tert*-butyl)-4,4-dimethoxycyclohexa-2,5-dien-1-one as illustrated in Scheme 31.[71]




**Scheme-31: Dienone-phenol rearrangement of 2-(*tert*-butyl)-4,4-dimethoxycyclohexa-2,5-dien-1-one**

As discussed earlier, the formation of the 1,4-dimethoxybenzene byproducts, albeit in small amounts, probably result from the further substitution of the 4-hydroxy-4-methoxycyclohexa-2,5-dien-1-one intermediates as shown in Scheme 32. Further reaction of the 1,4-dimethoxycyclohexa-2,5-diene-1,4-diol intermediates with acid to eliminate two molecules of water produces the respective 1,4-dimethoxybenzene products.




**Scheme-32: Formation 1,4-dimethoxybenzene products**

Interestingly, while it was possible to observe 1,4-dimethoxycyclohexa-2,5-diene-1,4-diol during these cross-over reactions, the corresponding 2-(*tert*-butyl)-1,4-dimethoxycyclohexa-2,5-diene-1,4-diol could not be observed. This is most probably the result of the rapid re-aromatisation of this intermediate (as a result of stereochemical crowding) to produce the final 2-(*tert*-butyl)-1,4-dimethoxybenzene.

## 2.4 Investigation of the reaction between 4-nitrosophenol with methanol in the presence of benzoquinone or hydroquinone

### 2.4.1 4-Nitrosophenol:benzoquinone/hydroquinone : Effect of mole ratio

In order to study the effect of the ratio of 4-nitrosophenol to benzoquinone (or hydroquinone) on the nature of reaction products and on the rate and extent of formation of reaction products during the reaction of 4-nitrosophenol:benzoquinone (or hydroquinone) mixtures with methanol in the presence of sulphuric acid as the acid catalyst, several experiments were carried out in which the respective amount of benzoquinone (or hydroquinone) was varied relative to 4-nitrosophenol. During these reactions the total amount of 4-nitrosophenol was kept constant at about 0.81 mmol and the amount of benzoquinone (or hydroquinone) in the reaction mixture was reduced from 0.81 mmol to 0.40 mmol, to 0.16 mmol and finally to 0.08 mmol to give approximate 4-nitrosophenol:benzoquinone (or hydroquinone) ratios of 1:1, 2:1, 5:1 and 10:1. The amount of acid catalyst (0.051g; 0.519 mmol) and the amount of methanol (20 mL) were kept constant in all the reactions, which were all carried out at a reaction temperature of $64^0$C. The results of these are summarised in Tables 2.38 – 2.45, and illustrated graphically in Figures 2.56-2.63.

**Table 2.38: 4-NOPh:BQ, Mole ratio = 1:1**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 14.19 | 48.72 | 35.71 | 1.38 |
| 5 | 5.82 | 48.15 | 43.78 | 2.25 |
| 10 | 1.02 | 45.38 | 48.61 | 4.99 |
| 15 | 0.94 | 43.67 | 47.53 | 7.86 |
| 30 | 0.85 | 42.09 | 44.16 | 12.90 |
| 60 | 0.23 | 39.92 | 41.56 | 18.29 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.39: 4-NOPh:BQ, Mole ratio = 2:1**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 66.6 | 33.3 | 0 | 0 |
| 2 | 14.09 | 32.50 | 52.20 | 1.21 |
| 5 | 7.37 | 30.22 | 59.13 | 3.28 |
| 10 | 0.40 | 28.22 | 65.94 | 5.44 |
| 15 | 0.33 | 27.54 | 64.71 | 7.42 |
| 30 | 0.30 | 29.09 | 60.14 | 10.47 |
| 60 | 0.25 | 25.44 | 57.18 | 17.13 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.40: 4-NOPh:BQ, Mole ratio = 5:1**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 83.3 | 16.6 | 0 | 0 |
| 2 | 14.39 | 15.94 | 68.43 | 1.14 |
| 5 | 8.15 | 15.39 | 74.56 | 1.91 |
| 10 | 1.52 | 13.45 | 81.68 | 3.25 |
| 15 | 0.86 | 12.16 | 82.64 | 4.24 |
| 30 | 0.24 | 10.93 | 82.55 | 6.18 |
| 60 | 0.05 | 8.43 | 82.41 | 9.01 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.41: 4-NOPh:BQ, Mole ratio = 10:1**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 90.9 | 9.0 | 0 | 0 |
| 2 | 10.07 | 8.85 | 80.76 | 0.13 |
| 5 | 3.59 | 8.3 | 87.21 | 0.80 |
| 10 | 1.70 | 7.89 | 89.18 | 1.13 |
| 15 | 0.85 | 6.95 | 90.02 | 2.08 |
| 30 | 0.47 | 5.38 | 90.43 | 3.62 |
| 60 | 0.09 | 3.86 | 90.81 | 5.14 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.42: 4-NOPh:HQ, Mole ratio = 1:1**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 12.45 | 32.38 | 37.31 | 3.39 | 14.47 |
| 5 | 8.67 | 30.23 | 41.25 | 4.71 | 15.14 |
| 10 | 7.59 | 24.82 | 42.11 | 6.83 | 18.65 |
| 15 | 7.18 | 17.45 | 41.38 | 9.64 | 24.35 |
| 30 | 3.76 | 10.58 | 39.55 | 14.65 | 31.46 |
| 60 | 1.87 | 3.74 | 38.12 | 21.26 | 35.01 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.43: 4-NOPh:HQ, Mole ratio = 2:1**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 66.6 | 33.3 | 0 | 0 | 0 |
| 2 | 19.41 | 15.28 | 46.72 | 1.49 | 17.0 |
| 5 | 18.27 | 15.83 | 47.33 | 3.42 | 15.05 |
| 10 | 15.24 | 14.02 | 51.26 | 7.63 | 11.75 |
| 15 | 12.08 | 12.38 | 52.94 | 9.84 | 12.66 |
| 30 | 8.18 | 7.66 | 51.42 | 13.28 | 19.36 |
| 60 | 3.25 | 4.31 | 50.38 | 17.96 | 24.0 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.44: 4-NOPh:HQ, Mole ratio = 5:1**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 83.3 | 16.6 | 0 | 0 | 0 |
| 2 | 15.18 | 9.22 | 68.02 | 1.19 | 6.29 |
| 5 | 13.87 | 8.03 | 68.76 | 2.14 | 7.10 |
| 10 | 12.35 | 5.92 | 69.15 | 4.33 | 8.15 |
| 15 | 10.56 | 4.13 | 71.14 | 6.75 | 7.32 |
| 30 | 6.44 | 1.98 | 70.86 | 9.41 | 11.21 |
| 60 | 2.83 | 0.61 | 72.47 | 14.03 | 9.96 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.45: 4-NOPh:HQ, Mole ratio = 10:1**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 90.9 | 9.0 | 0 | 0 | 0 |
| 2 | 9.17 | 3.18 | 81.70 | 0.27 | 5.58 |
| 5 | 8.42 | 1.85 | 82.18 | 0.84 | 6.61 |
| 10 | 6.13 | 1.12 | 83.09 | 1.68 | 7.88 |
| 15 | 5.06 | 0.58 | 85.14 | 2.43 | 6.69 |
| 30 | 3.55 | 0.15 | 84.65 | 4.97 | 6.58 |
| 60 | 1.93 | 0.06 | 86.27 | 7.18 | 4.46 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Figure 2.56: 4-NOPh:BQ (1:1 Mole ratio)**

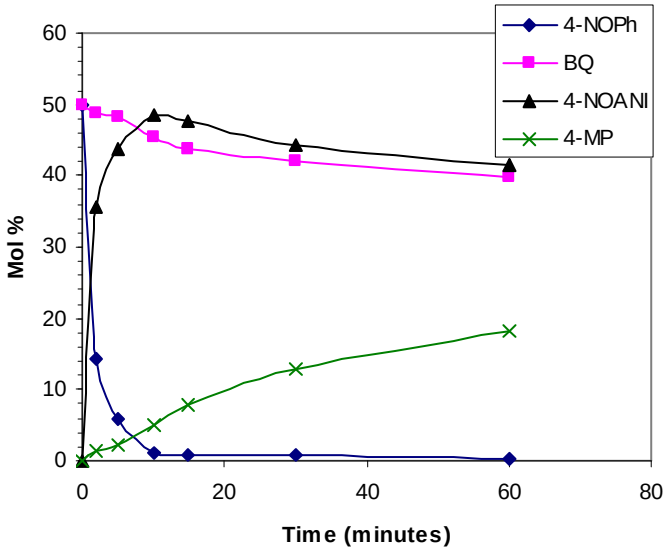



**Figure 2.57: 4-NOPh:HQ (1:1 Mole ratio)**

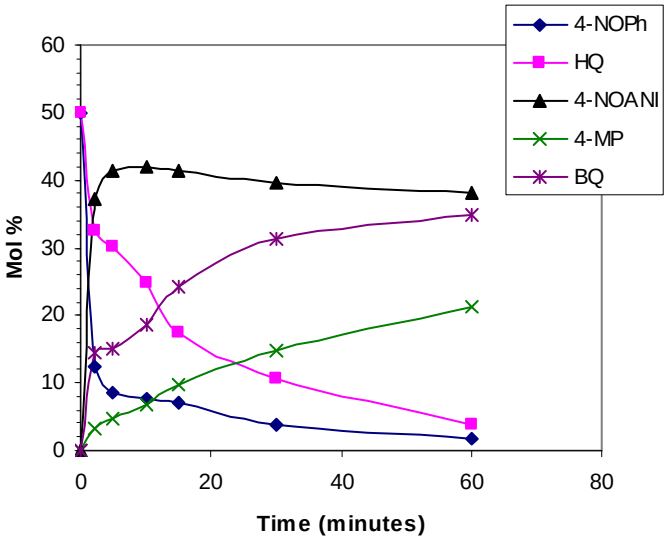



**Figure 2.58: 4-NOPh:BQ (2:1 Mole ratio)**

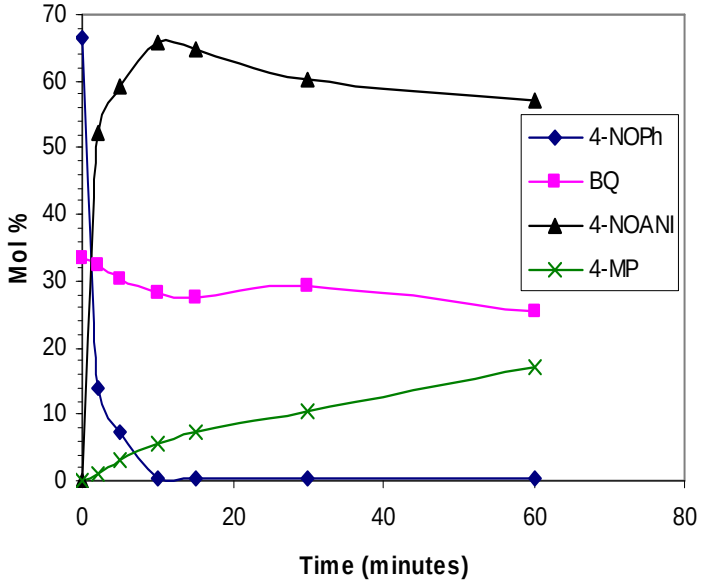



**Figure 2.59: 4-NOPh:HQ (2:1 Mole ratio)**

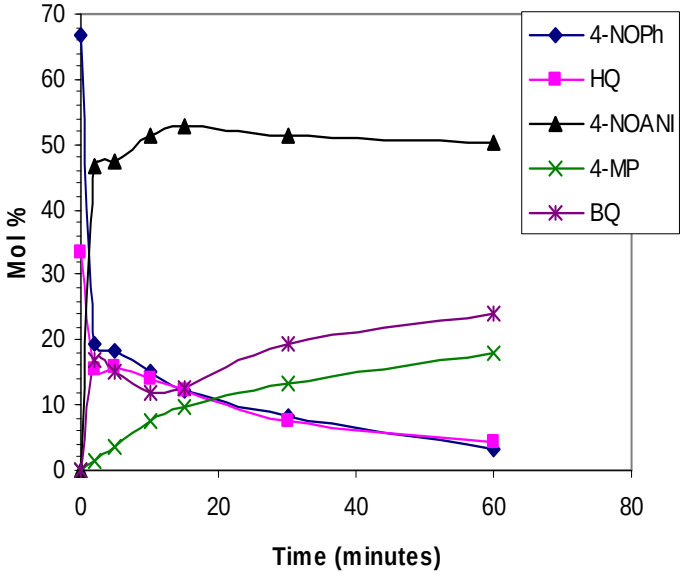


**Figure 2.60: 4-NOPh:BQ (5:1 Mole ratio)**

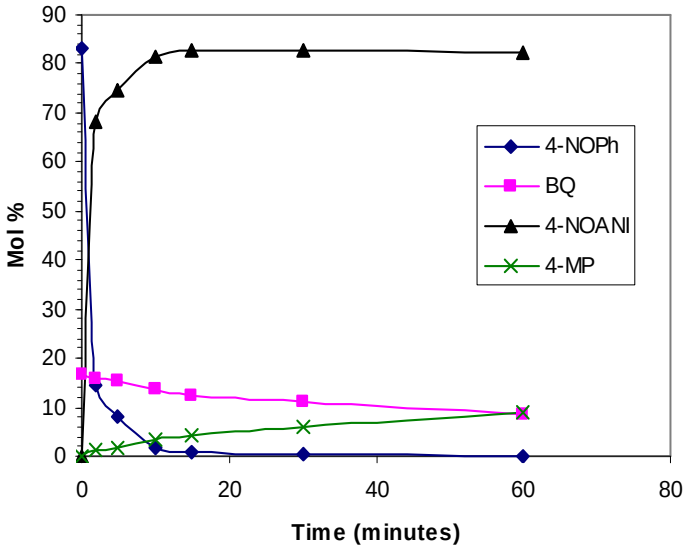



**Figure 2.61: 4-NOPh:HQ (5:1 Mole ratio)**

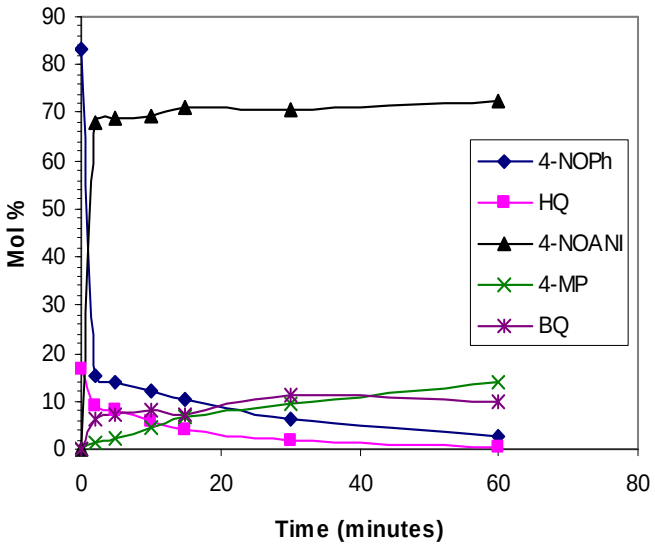



**Figure 2.62: 4-NOPh:BQ (10:1 Mole ratio)**

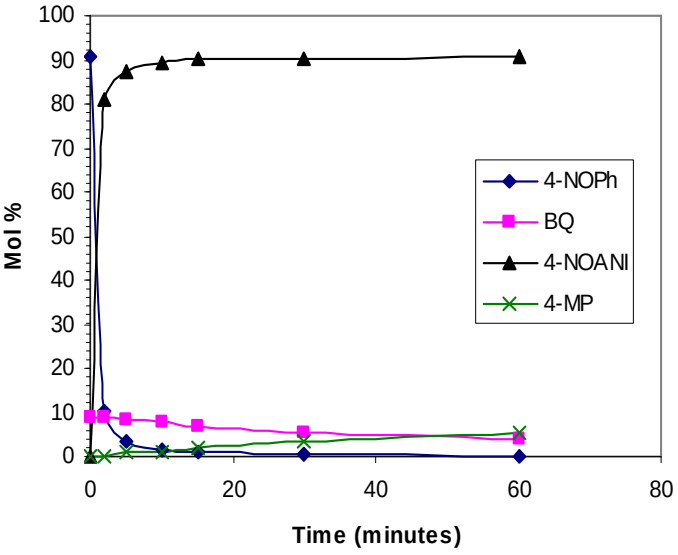
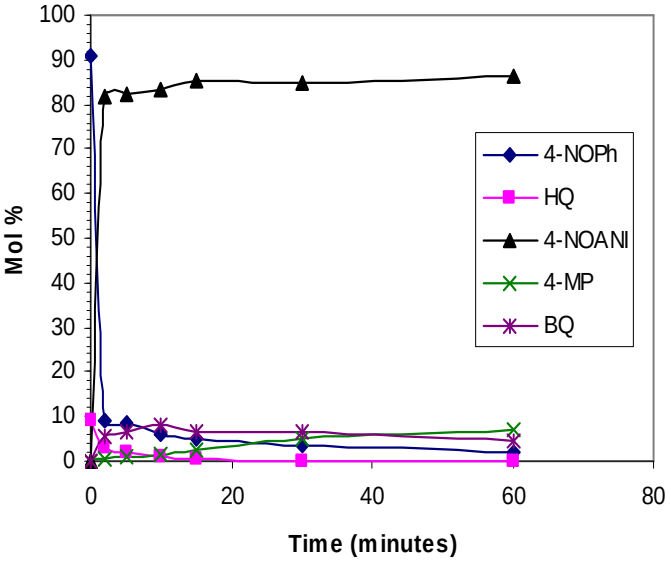



**Figure 2.63: 4-NOPh:HQ (10:1 Mole ratio)**



Several aspects regarding the above results deserve further comment. These are:

***Comparison with "Blank" Experiment:*** In the experiment in which 4-nitrosophenol was reacted with methanol in the absence of either hydroquinone or benzoquinone (Section 2.2.3), 4-nitrosoanisole was observed as the only reaction product. In all of the experiments where either benzoquinone or hydroquinone were additionally added, both hydroquinone (when benzoquinone was added), or benzoquinone (when hydroquinone was added) and 4-methoxyphenol were obtained as additional reaction products. This observation suggests the existence of a similar interaction between 4-nitrosophenol and benzoquinone (or hydroquinone) as has been discussed for hydroquinone and benzoquinone mixtures since neither benzoquinone nor hydroquinone reacts with methanol in the presence of sulphuric acid without some form of activation.

***Yield of 4-nitrosoanisole*:** When 4-nitrosophenol is reacted with methanol and sulphuric acid in the absence of benzoquinone (or hydroquinone) (Section 2.2.3), the yield of 4-nitrosoanisole is nearly quantitative. However, when either benzoquinone or hydroquinone is added initially with the 4-nitrosophenol, the yield of 4-nitrosoanisole is decreased significantly as is illustrated by the following summaries (Tables 2.46 and 2.47) of the preceding experiments.

**Table 2.46: 4-Nitrosoanisole yields with and without added benzoquinone**

| Mol ratio (4-NOPh/BQ) | 4-Nitrosoanisole (Mol %) |
|---|---|
| 1:0 | 94.27 |
| 1:1 | 41.56 |
| 2:1 | 57.18 |
| 5:1 | 82.41 |
| 10:1 | 90.81 |

**Table 2.47: 4-Nitrosoanisole yields with and without added hydroquinone**

| Mol ratio (4-NOPh/HQ) | 4-Nitrosoanisole (Mol %) |
|---|---|
| 1:0 | 94.27 |
| 1:1 | 38.12 |
| 2:1 | 50.38 |
| 5:1 | 72.47 |
| 10:1 | 86.27 |

The observed decrease in 4-nitrosoanisole yield is especially noticeable at higher benzoquinone (or hydroquinone) loadings. This implies that the effect of added benzoquinone (or hydroquinone) is either not very strong, being dependent upon the concentration of the added benzoquinone (or hydroquinone), or that the effect is continuously decreased by the "normal" reaction of benzoquinone in the presence of hydroquinone as soon as both are present in the reaction mixture.

It is also worth noting that during reactions where the amount of added benzoquinone (or hydroquinone) is relatively high, the yield of 4-nitrosoanisole starts to decrease after reaching some maximum value. This decrease in 4-nitrosoanisole content is, however, quite slow and cannot explain the significant drop in yield as compared to reactions in which no benzoquinone (or hydroquinone) was added.

***Yield of 4-methoxyphenol:*** The data summarized in Table 2.48 for the yield of 4-methoxyphenol obtained during these experiments show that the overall yield of 4-methoxyphenol decreases sharply as the amount of 4-nitrosophenol is increased relative to the amount of benzoquinone (or hydroquinone). However, when the yield of 4-methoxyphenol is calculated as a function of only the amount of benzoquinone (or hydroquinone) initially added, the yield increases sharply in the same direction. In all cases, irrespective of the initial ratio of 4-nitrosophenol to benzoquinone (or hydroquinone), the sum of 4-methoxyphenol, hydroquinone, and benzoquinone is always higher than the amount of benzoquinone (or hydroquinone) initially added. This clearly shows that at least some of the 4-

nitrosophenol has been converted into either 4-methoxyphenol or benzoquinone, or both.

**Table 2.48: Yield of 4-methoxyphenol**

| 4-NOPhOH:BQ Ratio | Yield 4-MP [% of total mmols 4-NOPhOH + BQ (or HQ)] | Yield 4-MP (% of mmols BQ (or HQ)) | % BQ | % HQ |
|---|---|---|---|---|
| 1:1 | 18.29 | 36.58 | 39.92 | - |
| 2:1 | 17.13 | 51.82 | 25.44 | - |
| 5:1 | 9.01 | 54.62 | 8.43 | - |
| 10:1 | 5.14 | 57.20 | 3.86 | - |
| **4-NOPhOH:HQ Ratio** | | | | |
| 1:1 | 21.26 | 42.52 | 35.01 | 3.74 |
| 2:1 | 17.96 | 54.33 | 24.00 | 4.31 |
| 5:1 | 14.03 | 85.06 | 9.96 | 0.61 |
| 10:1 | 7.18 | 79.88 | 4.46 | 0.06 |

### 2.4.2 4-Nitrosophenol:benzoquinone/hydroquinone: Effect of reaction temperature

In order to study the effect of reaction temperature on the rate and extent of formation of 4-nitrosoanisole and 4-methoxyphenol during the reaction of 4-nitrosophenol with methanol in the presence of hydroquinone (or benzoquinone) in the presence of sulphuric acid as acid catalyst, several experiments were carried out in which the reaction temperature was varied from the reflux temperature of methanol ($64^0$C) to room temperature. During these reactions, the 4-nitrosophenol:benzoquinone (or hydroquinone) mol ratio was kept constant at about 1:1 (0.81:0.81mmol). The temperature was reduced from reflux temperature to $50^0$C, to $30^0$C and finally to room temperature. The amount of acid catalyst (0.051g; 0.519mmol) and the amount of methanol (20 mL) were kept constant in all

the reactions. The results of these reactions are summarized in Tables 2.49 – 2.56, and illustrated graphically in Figures 2.64-2.71.

**Table 2.49: 4-NOPh:BQ, Reaction temperature= 64$^0$C (reflux temperature)**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 14.19 | 48.72 | 35.71 | 1.38 |
| 5 | 5.82 | 48.15 | 43.78 | 2.25 |
| 10 | 1.02 | 45.38 | 48.61 | 4.99 |
| 15 | 0.94 | 43.67 | 47.53 | 7.86 |
| 30 | 0.85 | 42.09 | 44.16 | 12.90 |
| 60 | 0.23 | 39.92 | 41.56 | 18.29 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.50: 4-NOPh:BQ, Reaction temperature= 50$^0$C**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 17.81 | 48.29 | 32.14 | 1.76 |
| 5 | 12.90 | 46.53 | 37.05 | 3.52 |
| 10 | 10.48 | 43.4 | 39.21 | 6.91 |
| 15 | 8.12 | 41.66 | 41.87 | 8.35 |
| 30 | 5.05 | 39.32 | 44.35 | 11.28 |
| 60 | 1.83 | 34.95 | 47.12 | 16.10 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.51: 4-NOPh:BQ, Reaction temperature= $30^0$C**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 35.43 | 49.94 | 14.57 | 0.06 |
| 5 | 31.64 | 49.68 | 18.34 | 0.34 |
| 10 | 28.37 | 48.97 | 21.53 | 1.13 |
| 15 | 25.84 | 49.16 | 23.15 | 1.85 |
| 30 | 20.73 | 48.13 | 28.36 | 2.78 |
| 60 | 16.58 | 47.46 | 31.44 | 4.52 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.52: 4-NOPh:BQ, Reaction temperature= room temperature**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 41.23 | 49.99 | 8.76 | 0.02 |
| 5 | 37.76 | 49.95 | 12.24 | 0.05 |
| 10 | 33.57 | 49.91 | 16.41 | 0.11 |
| 15 | 29.18 | 49.71 | 20.79 | 0.32 |
| 30 | 23.85 | 49.36 | 26.14 | 0.65 |
| 60 | 18.68 | 49.16 | 31.29 | 0.87 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.53: 4-NOPh:HQ, Reaction temperature= 64$^0$C (reflux temperature)**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 12.45 | 32.38 | 37.31 | 3.39 | 14.47 |
| 5 | 8.67 | 30.23 | 41.25 | 4.71 | 15.14 |
| 10 | 7.59 | 24.82 | 42.11 | 6.83 | 18.65 |
| 15 | 7.18 | 17.45 | 41.38 | 9.64 | 24.35 |
| 30 | 3.76 | 10.58 | 39.55 | 14.65 | 31.46 |
| 60 | 1.87 | 3.74 | 38.12 | 21.26 | 35.01 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.54: 4-NOPh:HQ, Reaction temperature= 50$^0$C**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 24.63 | 36.57 | 25.27 | 1.17 | 12.36 |
| 5 | 22.32 | 34.89 | 27.08 | 3.92 | 11.79 |
| 10 | 18.77 | 30.23 | 30.52 | 5.76 | 14.72 |
| 15 | 16.85 | 26.12 | 32.13 | 7.89 | 17.01 |
| 30 | 11.42 | 19.76 | 35.54 | 13.84 | 19.44 |
| 60 | 3.51 | 7.68 | 41.69 | 17.29 | 29.83 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.55: 4-NOPh:HQ, Reaction temperature= $30^0$C**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 37.56 | 48.33 | 12.41 | 0.36 | 1.34 |
| 5 | 33.21 | 48.06 | 16.78 | 1.08 | 0.87 |
| 10 | 29.42 | 47.15 | 20.53 | 2.19 | 0.71 |
| 15 | 25.77 | 45.61 | 24.03 | 3.73 | 0.86 |
| 30 | 21.18 | 42.03 | 27.18 | 4.88 | 4.73 |
| 60 | 14.95 | 40.81 | 32.05 | 7.05 | 5.14 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.56: 4-NOPh:HQ, Reaction temperature= room temperature**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 43.27 | 48.05 | 6.71 | 0.65 | 1.32 |
| 5 | 42.53 | 47.12 | 7.46 | 0.87 | 2.02 |
| 10 | 39.84 | 45.96 | 10.06 | 1.03 | 3.11 |
| 15 | 36.62 | 43.15 | 12.35 | 1.17 | 6.71 |
| 30 | 30.07 | 40.87 | 18.91 | 1.76 | 8.39 |
| 60 | 21.45 | 36.53 | 27.87 | 1.89 | 12.26 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Figure 2.64: 4-NOPh:BQ, RT= 64$^0$C**

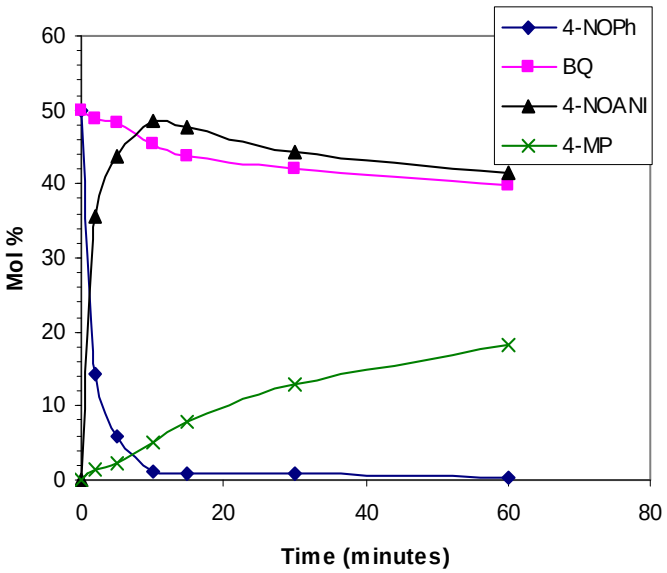



**Figure 2.65: 4-NOPh:HQ, RT= 64$^0$C**

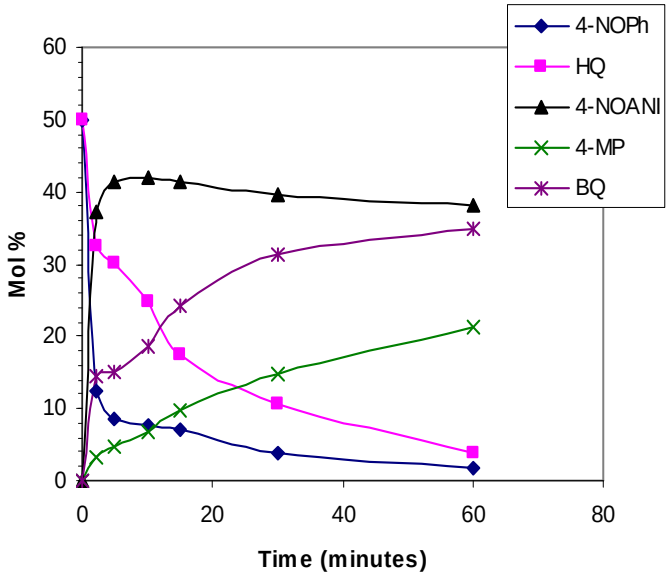



**Figure 2.66: 4-NOPh:BQ, RT= 50$^0$C**

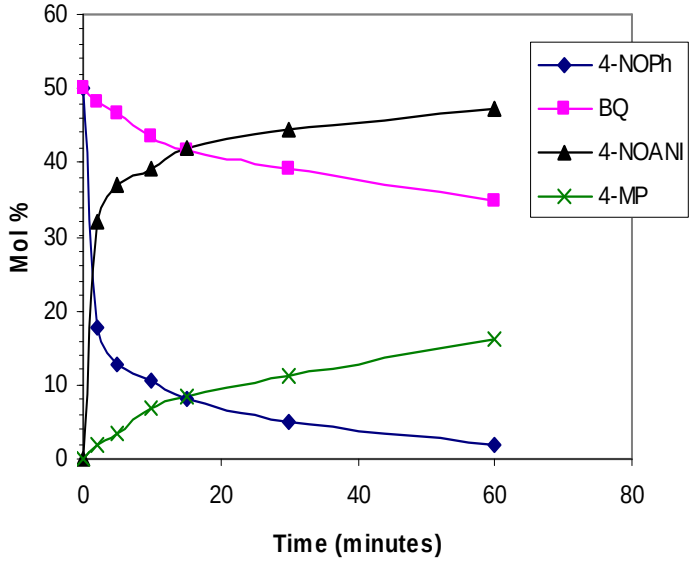



**Figure 2.67: 4-NOPh:HQ, RT= 50$^0$C**

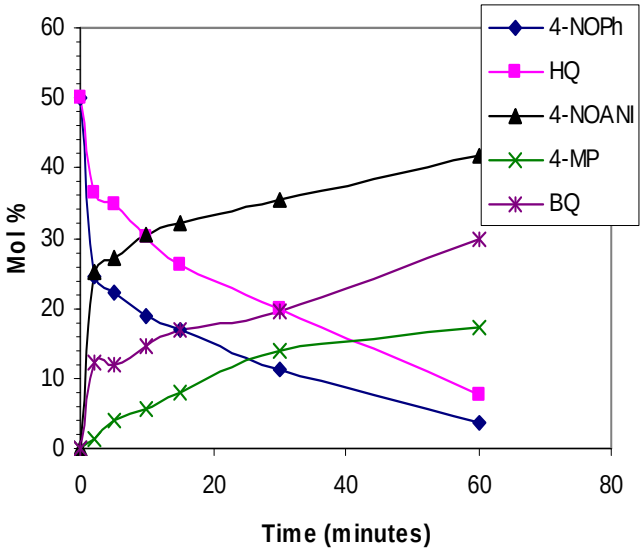


**Figure 2.68: 4-NOPh:BQ, RT= 30$^0$C**

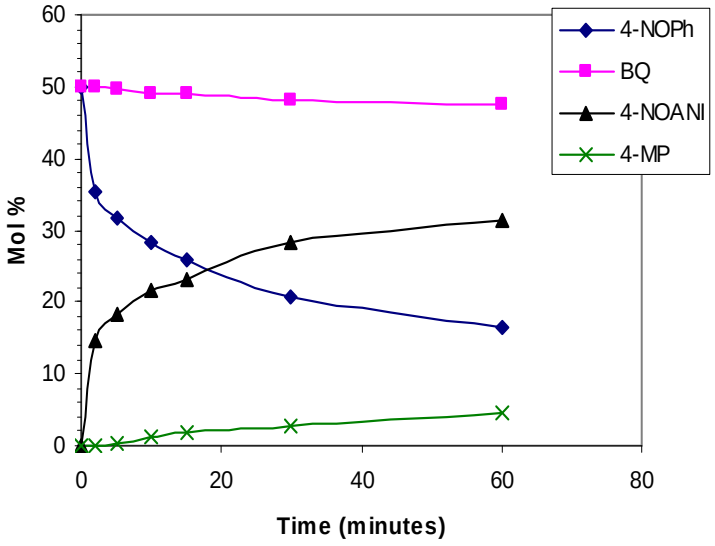



**Figure 2.69: 4-NOPh:HQ, RT= 30$^0$C**

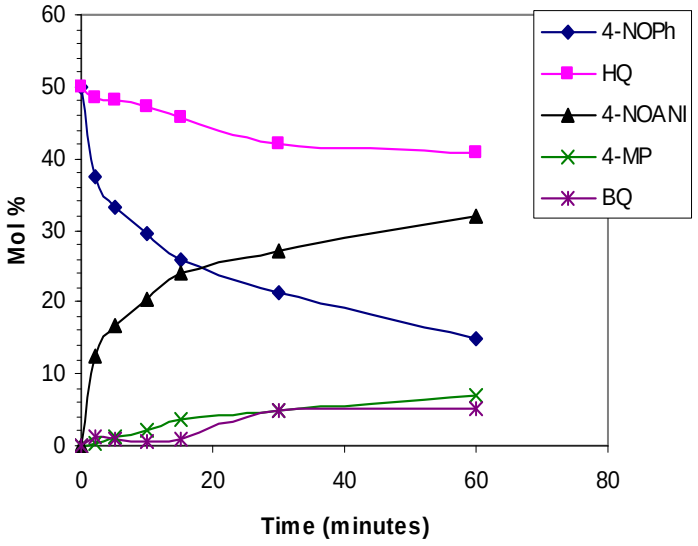



**Figure 2.70: 4-NOPh:BQ, RT= Room temp**

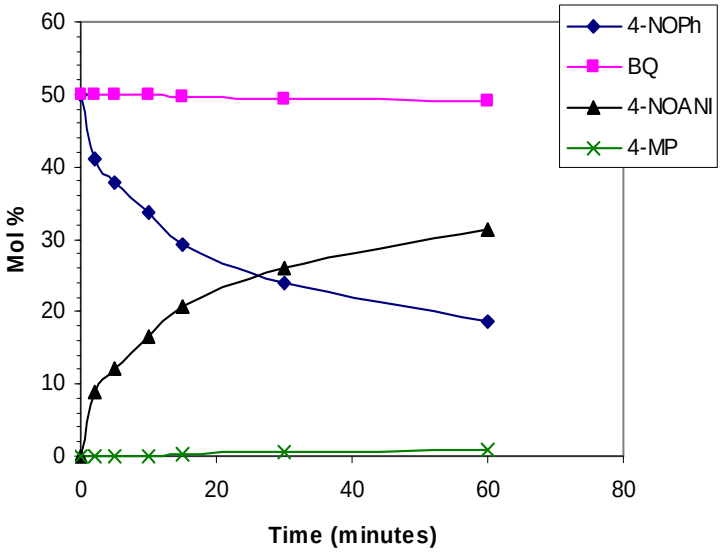
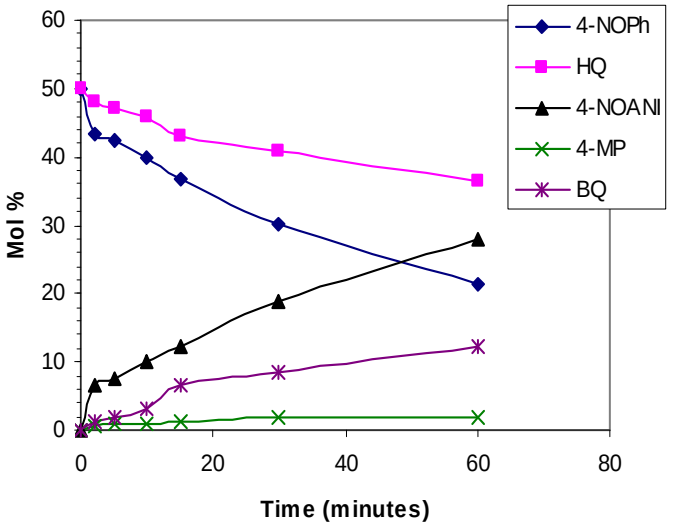



**Figure 2.71: 4-NOPh:HQ, RT= Room temp**




The results obtained for the above temperature experiments show that the most noticeable effect of temperature is to decrease the rate of all the reactions occurring as the temperature is decreased. From the results shown in Tables 2.49 to 2.56, it is not clear whether some reactions are affected to a lesser or higher

degree by a change in temperature. However, the previously observed decrease in 4-methoxyanisole yield at longer reaction times is not observed at temperatures of $50^0$C or lower.

### 2.4.3 4-Nitrosophenol:benzoquinone/hydroquinone: Effect of acid catalyst concentration

In these reactions, the effect of increasing acid catalyst [conc. $H_2SO_4$ (18M)] concentration on the rate and extent of formation of reaction products during the reaction of 4-nitrosophenol in the presence of benzoquinone (or hydroquinone) with methanol was studied at the reflux temperature of methanol (64 $^0$C). Several experiments were carried out in which the amount of acid catalyst was progressively increased from 0.051g to 0.357g. During these reactions the 4-nitrosophenol:benzoquinone (or hydroquinone) mol ratio was kept constant at about 1:1 (0.81:0.81mmol). The amount of acid was increased from 0.051g (0.519mmol) to 0.102g (1.038mmol), to 0.153g (1.557mmol), to 0.255g (2.595mmol) and finally to 0.357g (3.633mmol). The amount of methanol (20 mL) and the reaction temperature of 64 $^0$C were kept constant in all the reactions. The results of these are summarized in Tables 2.57 – 2.66, and illustrated graphically in Figures 2.72-2.81.

**Table 2.57: 4-NOPh:BQ, Concentration of acid catalyst= 0.051g**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 14.19 | 48.72 | 35.71 | 1.38 |
| 5 | 5.82 | 48.15 | 43.78 | 2.25 |
| 10 | 1.02 | 45.38 | 48.61 | 4.99 |
| 15 | 0.94 | 43.67 | 47.53 | 7.86 |
| 30 | 0.85 | 42.09 | 44.16 | 12.90 |
| 60 | 0.23 | 39.92 | 41.56 | 18.29 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.58: 4-NOPh:BQ, Concentration of acid catalyst= 0.102g**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 25.15 | 47.04 | 24.62 | 3.19 |
| 5 | 21.66 | 46.13 | 26.34 | 5.87 |
| 10 | 17.54 | 44.48 | 29.36 | 8.62 |
| 15 | 13.19 | 41.04 | 33.83 | 11.94 |
| 30 | 6.24 | 38.41 | 38.76 | 16.59 |
| 60 | 0.26 | 33.38 | 42.84 | 23.52 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.59: 4-NOPh:BQ, Concentration of acid catalyst= 0.153g**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 19.28 | 44.76 | 29.71 | 6.25 |
| 5 | 15.49 | 43.85 | 31.54 | 9.12 |
| 10 | 11.35 | 38.13 | 35.63 | 14.89 |
| 15 | 8.22 | 36.63 | 36.48 | 18.67 |
| 30 | 1.87 | 35.22 | 42.13 | 20.78 |
| 60 | 0.02 | 30.45 | 45.18 | 24.35 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.60: 4-NOPh:BQ, Concentration of acid catalyst= 0.255g**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 12.62 | 45.94 | 37.28 | 4.16 |
| 5 | 9.15 | 44.9 | 40.16 | 5.79 |
| 10 | 7.28 | 42.74 | 41.53 | 8.45 |
| 15 | 4.32 | 40.35 | 42.76 | 12.57 |
| 30 | 0.21 | 37.13 | 45.93 | 16.73 |
| 60 | 0.04 | 34.87 | 44.25 | 20.84 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.61: 4-NOPh:BQ, Concentration of acid catalyst= 0.357g**

| Time (minutes) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 2 | 6.27 | 47.76 | 40.63 | 5.34 |
| 5 | 3.63 | 44.59 | 43.56 | 8.22 |
| 10 | 1.39 | 43.00 | 45.18 | 10.43 |
| 15 | 0.82 | 42.27 | 43.62 | 13.29 |
| 30 | 0.03 | 42.84 | 41.19 | 15.94 |
| 60 | 0.01 | 38.95 | 42.38 | 18.66 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.62: 4-NOPh:HQ, Concentration of acid catalyst= 0.051g**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 12.45 | 32.38 | 37.31 | 3.39 | 14.47 |
| 5 | 8.67 | 30.23 | 41.25 | 4.71 | 15.14 |
| 10 | 7.59 | 24.82 | 42.11 | 6.83 | 18.65 |
| 15 | 7.18 | 17.45 | 41.38 | 9.64 | 24.35 |
| 30 | 3.76 | 10.58 | 39.55 | 14.65 | 31.46 |
| 60 | 1.87 | 3.74 | 38.12 | 21.26 | 35.01 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.63: 4-NOPh:HQ, Concentration of acid catalyst= 0.102g**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 27.32 | 18.14 | 22.62 | 5.26 | 26.66 |
| 5 | 23.15 | 13.66 | 26.84 | 7.32 | 29.03 |
| 10 | 19.86 | 8.63 | 28.41 | 10.85 | 32.25 |
| 15 | 15.73 | 5.50 | 33.83 | 14.79 | 30.15 |
| 30 | 5.08 | 1.02 | 37.95 | 19.63 | 36.32 |
| 60 | 0.05 | 0.18 | 41.17 | 25.12 | 33.48 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.64: 4-NOPh:HQ, Concentration of acid catalyst = 0.153g**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 15.65 | 18.50 | 32.45 | 5.02 | 28.38 |
| 5 | 11.39 | 14.01 | 35.16 | 6.59 | 32.85 |
| 10 | 9.30 | 6.79 | 39.12 | 8.87 | 35.92 |
| 15 | 8.63 | 3.37 | 41.32 | 13.52 | 33.16 |
| 30 | 0.33 | 0.32 | 42.76 | 18.16 | 38.43 |
| 60 | 0.14 | 0.21 | 40.86 | 24.19 | 34.60 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.65: 4-NOPh:HQ, Concentration of acid catalyst = 0.255g**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 12.15 | 13.66 | 36.54 | 3.54 | 34.11 |
| 5 | 10.68 | 7.59 | 38.32 | 6.95 | 36.46 |
| 10 | 9.19 | 4.60 | 39.12 | 8.15 | 38.94 |
| 15 | 8.07 | 2.62 | 40.72 | 11.25 | 37.34 |
| 30 | 0.45 | 0.08 | 44.26 | 15.87 | 39.34 |
| 60 | 0.03 | 0.05 | 42.64 | 21.07 | 36.21 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Table 2.66: 4-NOPh:HQ, Concentration of acid catalyst = 0.357g**

| Time (minutes) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 2 | 8.75 | 9.83 | 40.62 | 2.59 | 38.21 |
| 5 | 5.01 | 7.65 | 44.21 | 5.26 | 37.87 |
| 10 | 2.55 | 3.16 | 45.73 | 6.85 | 41.71 |
| 15 | 1.74 | 1.23 | 43.55 | 10.41 | 43.07 |
| 30 | 0.09 | 0.14 | 41.28 | 14.68 | 43.81 |
| 60 | 0.01 | 0.02 | 40.79 | 19.33 | 39.85 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Figure 2.72: 4-NOPh:BQ, acid= 0.051g**

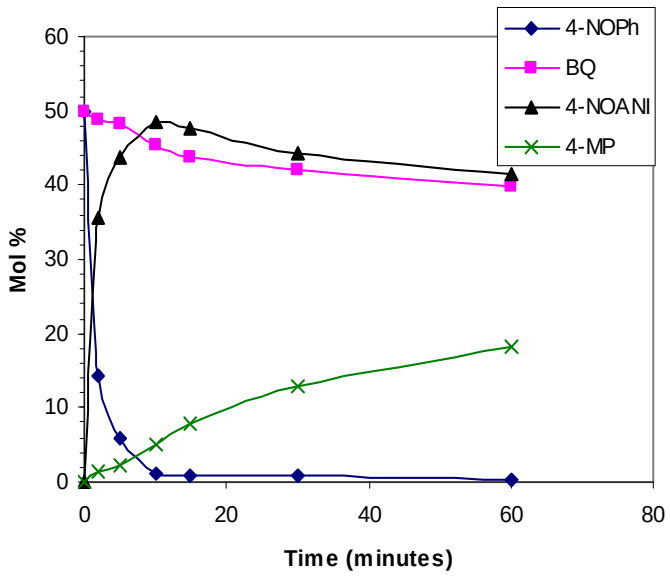



**Figure 2.73: 4-NOPh:HQ, acid= 0.051g**

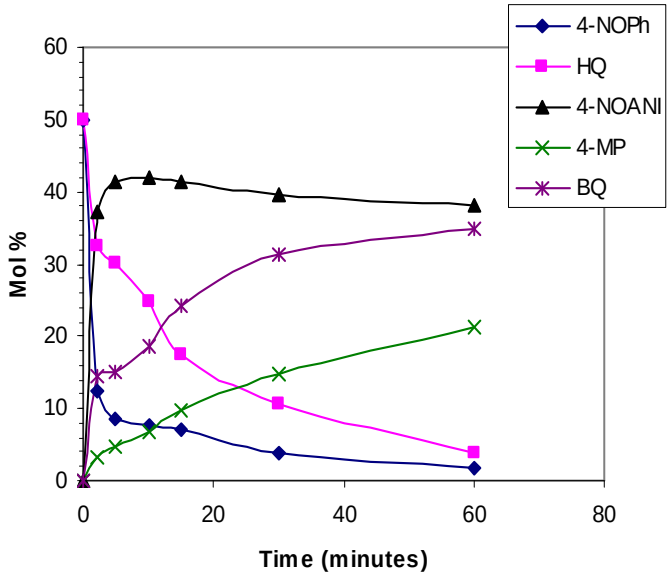


**Figure 2.74: 4-NOPh:BQ, acid= 0.102g**

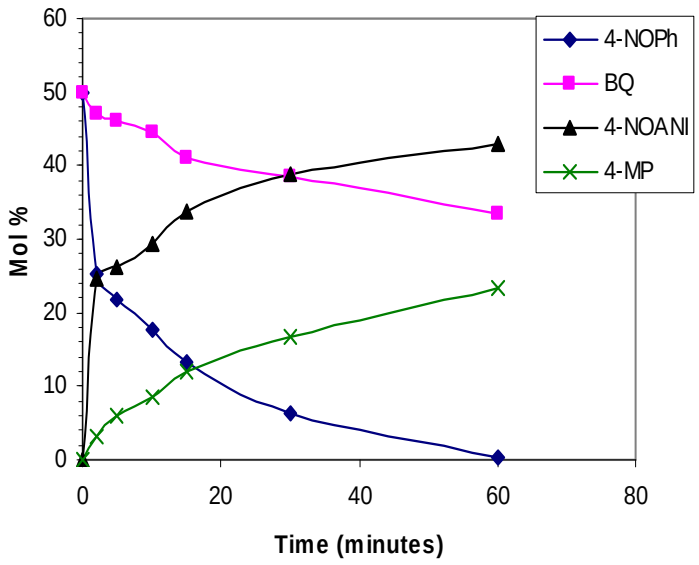



**Figure 2.75: 4-NOPh:HQ, acid= 0.102g**

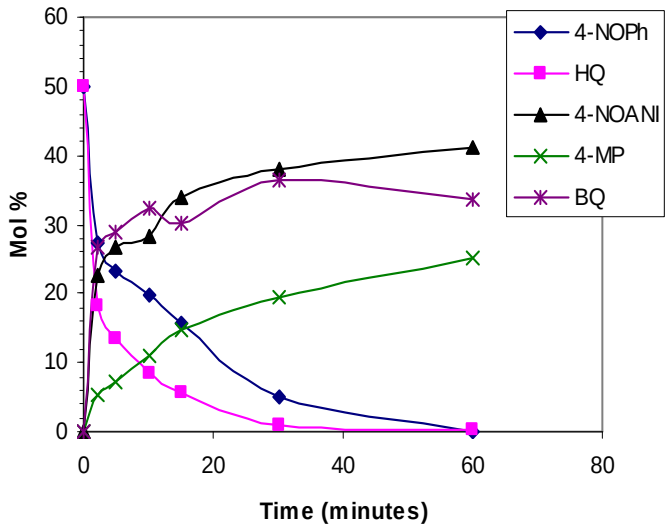



**Figure 2.76: 4-NOPh:BQ, acid= 0.153g**

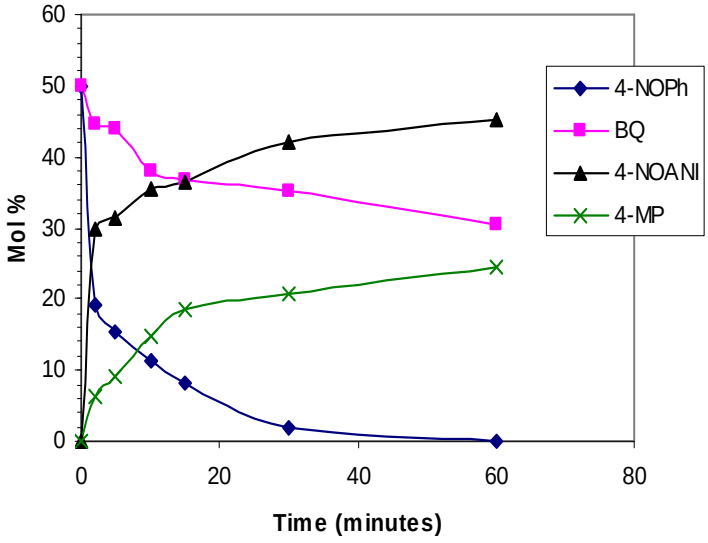



**Figure 2.77: 4-NOPh:HQ, acid= 0.153g**

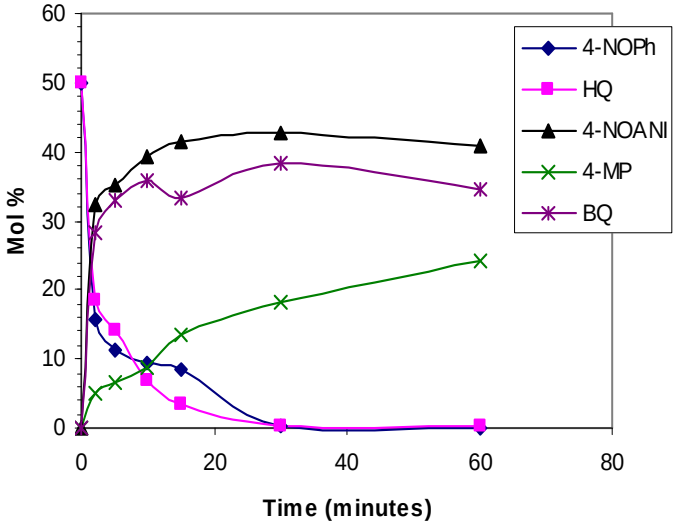


**Figure 2.78: 4-NOPh:BQ, acid= 0.255g**

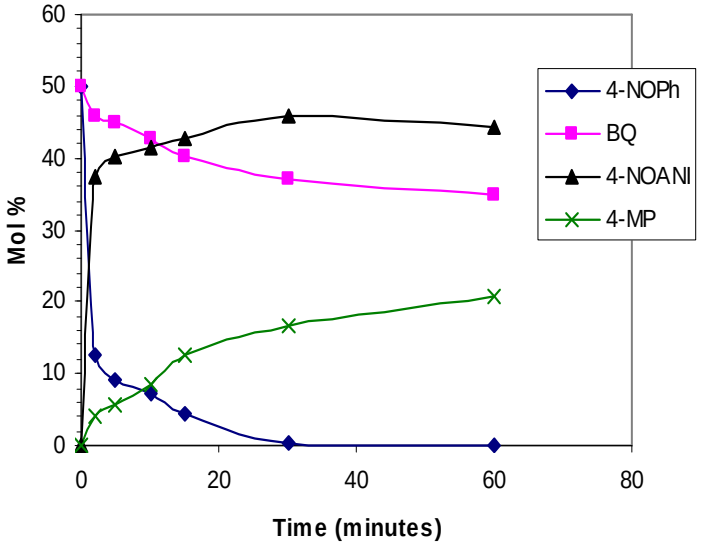



**Figure 2.79: 4-NOPh:HQ, acid= 0.255g**

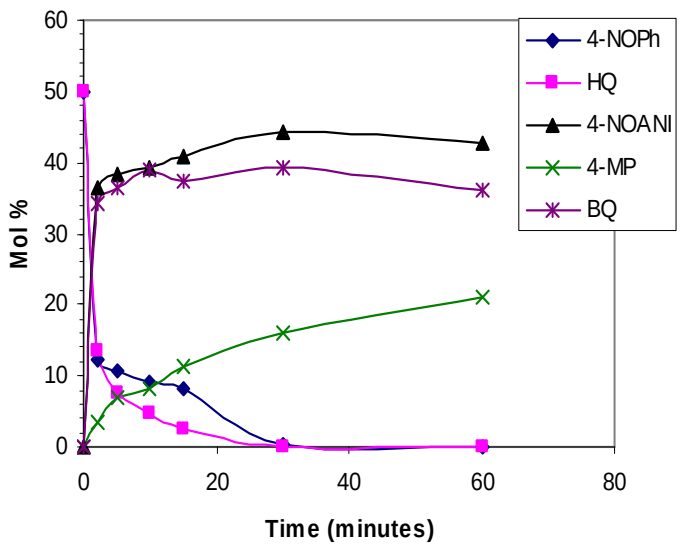



**Figure 2.80: 4-NOPh:BQ, acid= 0.357g**

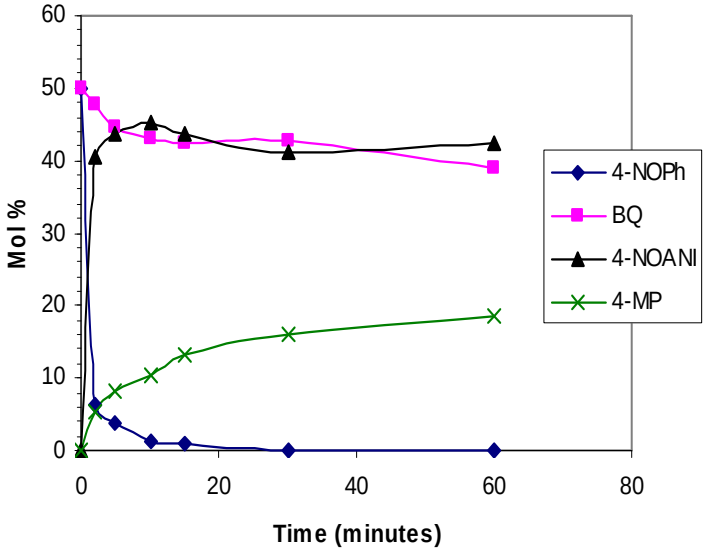
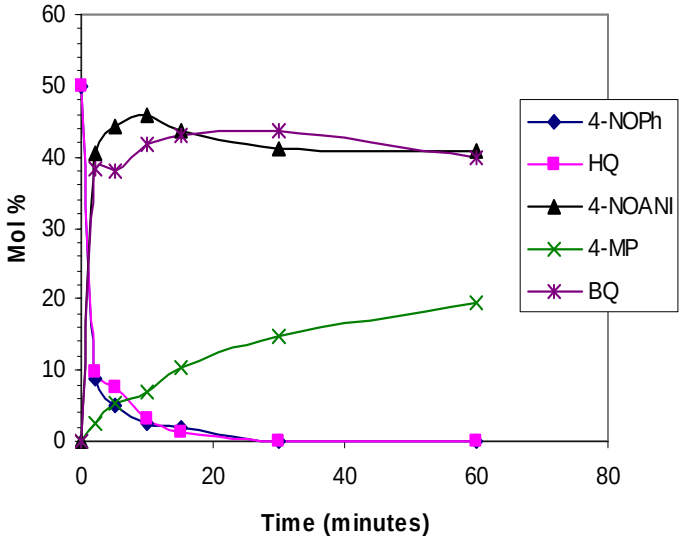



**Figure 2.81: 4-NOPh:HQ, acid= 0.357g**




In contrast to the effect of increasing acid concentration on the rate and extent of the reaction of hydroquinone (in the presence of benzoquinone) with methanol,

increasing the acid concentration in the above reactions has surprisingly little effect, if any, on either the rate of reaction or the extent of reaction. This observation is clearly illustrated by the following summary (Table 2.67) of these results.

**Table 2.67: Summary of acid catalyst concentration study (values for hydroquinone experiments are in brackets)**

| Acid catalyst (g) | 4-NOANI*** (Mol %) | BQ** (Mol %) | HQ*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0.051 | 41.56 (38.12) | 39.92 (35.01) | - (3.74) | 18.29 (21.26) |
| 0.102 | 42.84 (41.17) | 33.38 (33.48) | - (0.18) | 23.52 (25.12) |
| 0.153 | 45.18 (40.86) | 30.45 (34.60) | - (0.21) | 24.35 (24.19) |
| 0.255 | 44.25 (42.64) | 34.87 (36.21) | - (0.05) | 20.84 (21.07) |
| 0.357 | 42.38 (40.79) | 38.95 (39.85) | - (0.02) | 18.66 (19.33) |

### 2.4.4 4-Nitrosophenol:benzoquinone (or hydroquinone): Effect of reaction time

In order to investigate the effect of increasing reaction time on the extent of formation of products during the reaction of 4-nitrosophenol in the presence of benzoquinone (or hydroquinone), mixtures of 4-nitrosophenol and benzoquinone (or hydroquinone) were reacted with methanol at the reflux temperature (64 $^0$C) of methanol for different periods of time. The 4-nitrosophenol:benzoquinone (or hydroquinone) mol ratio, 1:1 (0.4:0.4mmol) and the amount of acid catalyst, 0.051g (0.519mmol) were kept constant. The amount of methanol (20 mL) and the reaction temperature of 64 $^0$C were also kept constant in both the reactions. The reactions were run for 10 hours. The results of these are summarized in Tables 2.68 and 2.69, and illustrated graphically in Figures 2.82 and 2.83.

**Table 2.68: 4-NOPh:BQ, Reaction time= 10 hours (time effect)**

| Time (hours) | 4-NOPh* (Mol %) | BQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) |
|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 |
| 1 | 3.42 | 36.45 | 39.96 | 20.17 |
| 2 | 0.14 | 33.54 | 37.76 | 28.56 |
| 3 | 0.01 | 30.25 | 34.30 | 35.44 |
| 4 | 0 | 27.08 | 32.06 | 40.86 |
| 5 | 0 | 25 | 30.98 | 44.02 |
| 10 | 0 | 24.03 | 24.76 | 51.21 |

*4-NOPh= 4-nitrosophenol; **BQ= benzoquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol

**Table 2.69: 4- NOPh:HQ, Reaction time= 10 hours (time effect)**

| Time (hours) | 4-NOPh* (Mol %) | HQ** (Mol %) | 4-NOANI*** (Mol %) | 4-MP**** (Mol %) | BQ***** (Mol %) |
|---|---|---|---|---|---|
| 0 | 50 | 50 | 0 | 0 | 0 |
| 1 | 2.87 | 33.18 | 36.89 | 18.83 | 8.23 |
| 2 | 0.09 | 30.15 | 34.56 | 29.05 | 6.15 |
| 3 | 0.03 | 29.03 | 32.94 | 34.89 | 3.11 |
| 4 | 0 | 27.05 | 30.41 | 42.54 | 0 |
| 5 | 0 | 25.20 | 27.78 | 47.02 | 0 |
| 10 | 0 | 20.26 | 23.53 | 56.21 | 0 |

*4-NOPh= 4-nitrosophenol; **HQ= hydroquinone; ***4-NOANI= 4-nitrosoanisole; ****4-MP= 4-methoxyphenol; *****BQ= benzoquinone

**Figure 2.82: 4-NOPh:BQ, Reaction time =10h**

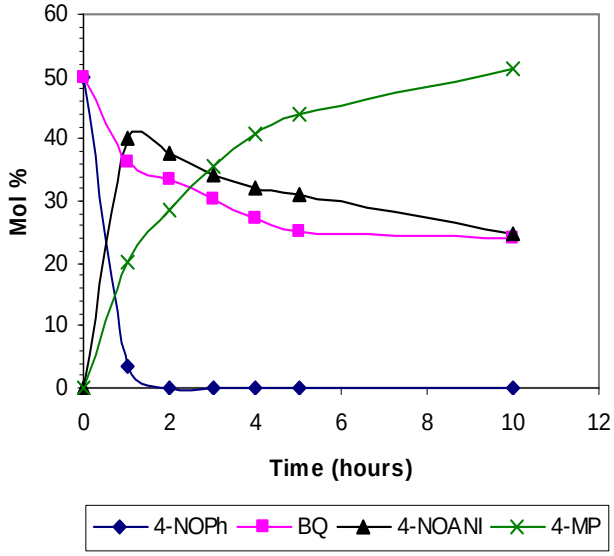
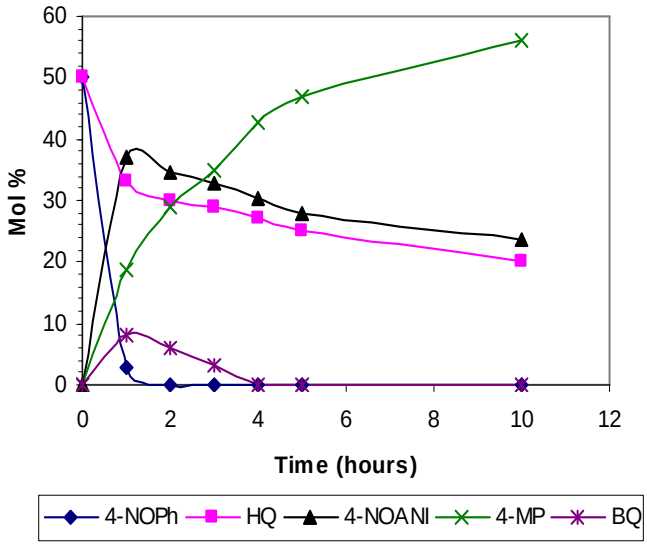



**Figure 2.83: 4-NOPh:HQ, Reaction time =10h**




In comparison to reactions that were run for only one hour, these extended period reactions show a significant increase in the yield of 4-methoxyphenol. This increase in 4-methoxyphenol yield is accompanied by a simultaneous decrease in the yield of 4-nitrosoanisole, and the increased yield of 4-methoxyphenol can probably be ascribed (at least in part) to the slow conversion of initially formed 4-nitrosoanisole. In the case where 4-nitrosophenol is reacted in the presence of hydroquinone, initially formed benzoquinone will also interact with hydroquinone to form 4-methoxyphenol as discussed previously.

### 2.4.5 Reaction between 4-nitrosophenol and 2-*tert*-butylhydroquinone

In an attempt to gain further information regarding the course of the reaction when methanol is reacted with 4-nitrosophenol in the presence of either a hydroquinone or benzoquinone in the presence of an acid catalyst, a cross-over reaction similar to the ones described for the hydroquinone/benzoquinone reaction was carried out where 4-nitrosophenol was reacted with methanol in the presence of 2-*tert*-butylhydroquinone. In this reaction, 0.91 mmol (0.151g) of 2-*tert*-butylhydroquinone and 0.91mmol (0.112g) of 4-nitrosophenol were reacted with methanol (20mL) to which 0.051g (0.519mmol) of concentrated $H_2SO_4$ (18M) was added and the

reaction temperature maintained at 64 $^0$C. Aliquots of the reaction mixture were taken at regular intervals so as to be able to study the nature of intermediates present in the reaction mixture by means of trace GC-MS techniques.

Figure 2.84 depicts the GC-MS chromatogram obtained for the reaction mixture after a reaction time of 2 minutes, while Figure 2.85 depicts the chromatogram obtained for the reaction mixture after a reaction time of 60 minutes. The identities of the peaks numbered 1 – 8 in Figure 2.84 have been assigned on the basis of their respective mass fragmentation patterns as shown in Figures 2.86-2.93.

**Figure 2.84: GC-MS chromatogram (2-*t*-butylhydroquinone reaction):**

**Reaction time = 2 minutes**

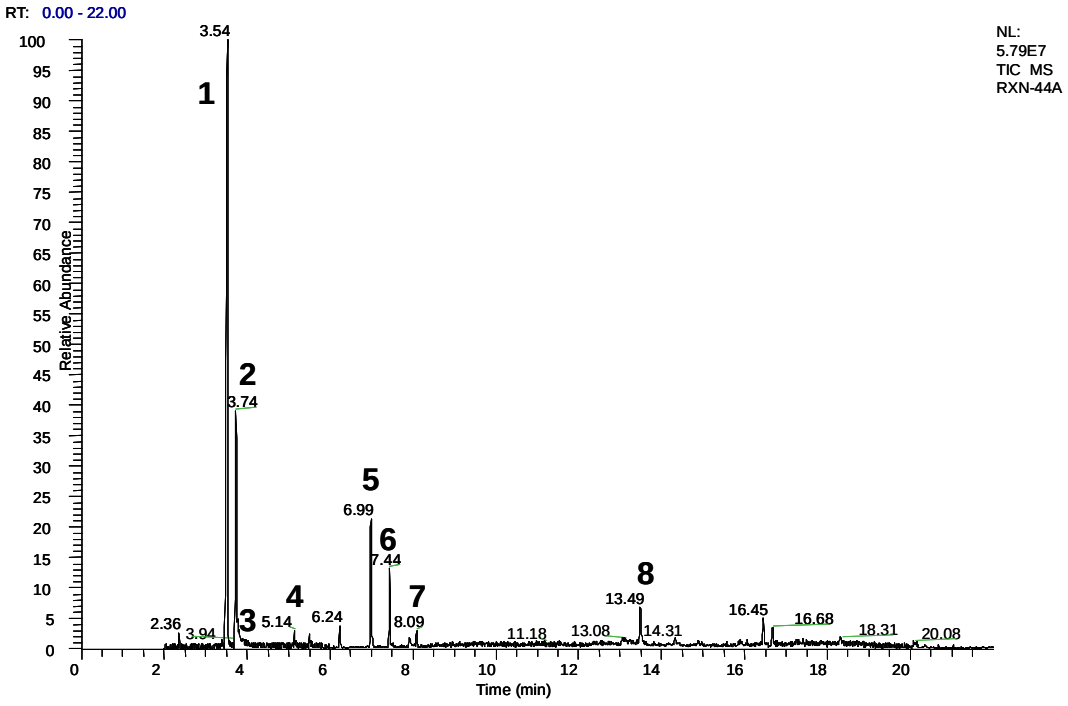


**Figure 2.85: GC-MS chromatogram (2-*t*-butylhydroquinone reaction):**

**Reaction time = 60 minutes**

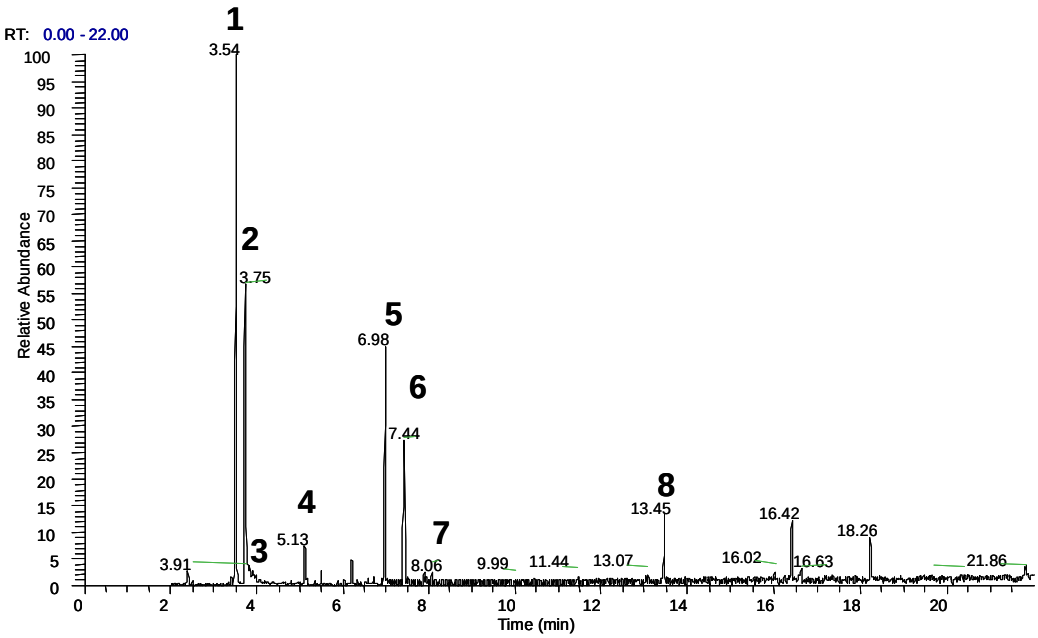



**Figure 2.86: Mass fragmentation pattern: Peak No. 1**

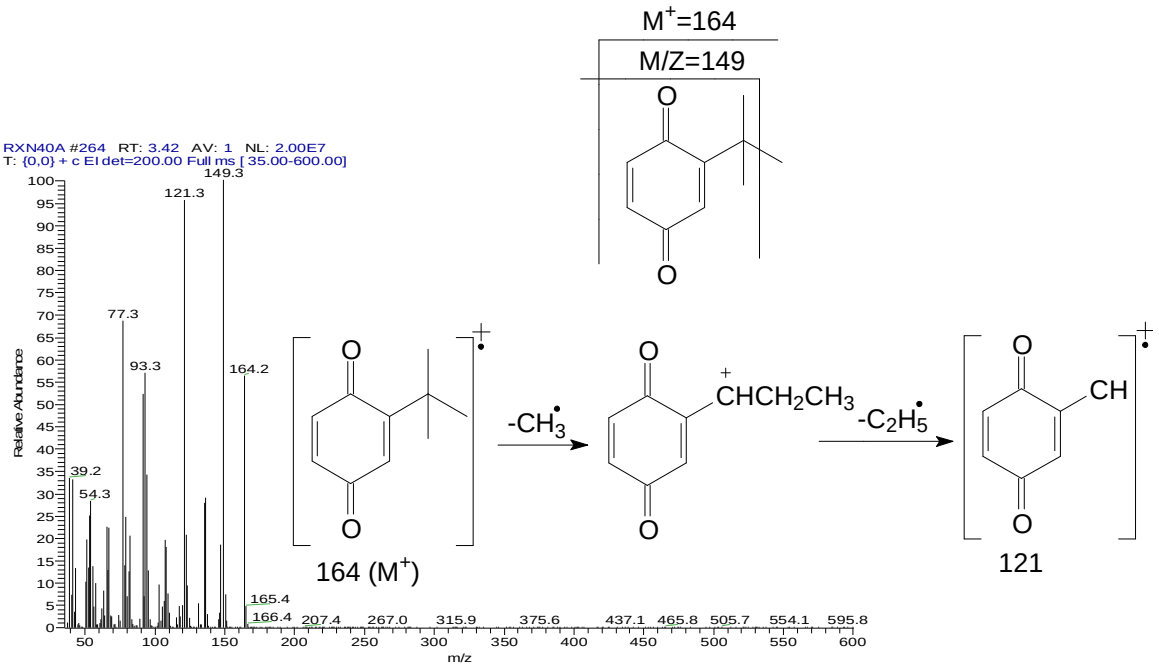


**Figure 2.87: Mass fragmentation pattern: Peak No. 2**

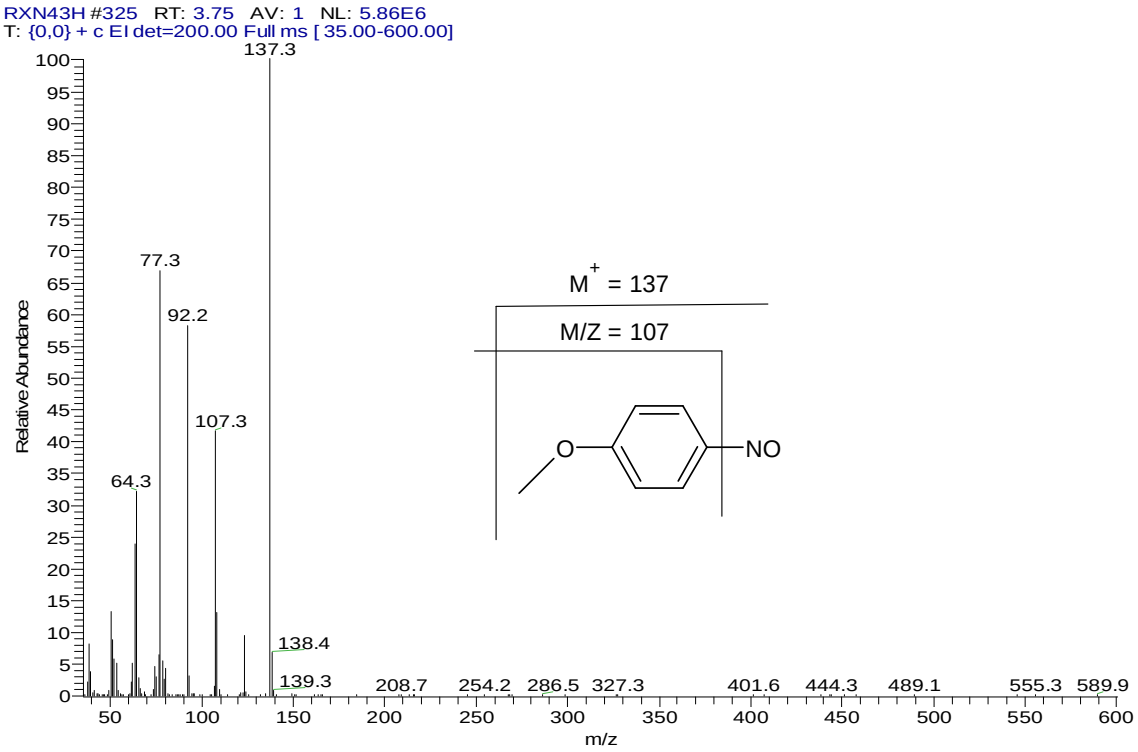



**Figure 2.88: Mass fragmentation pattern: Peak No. 3**

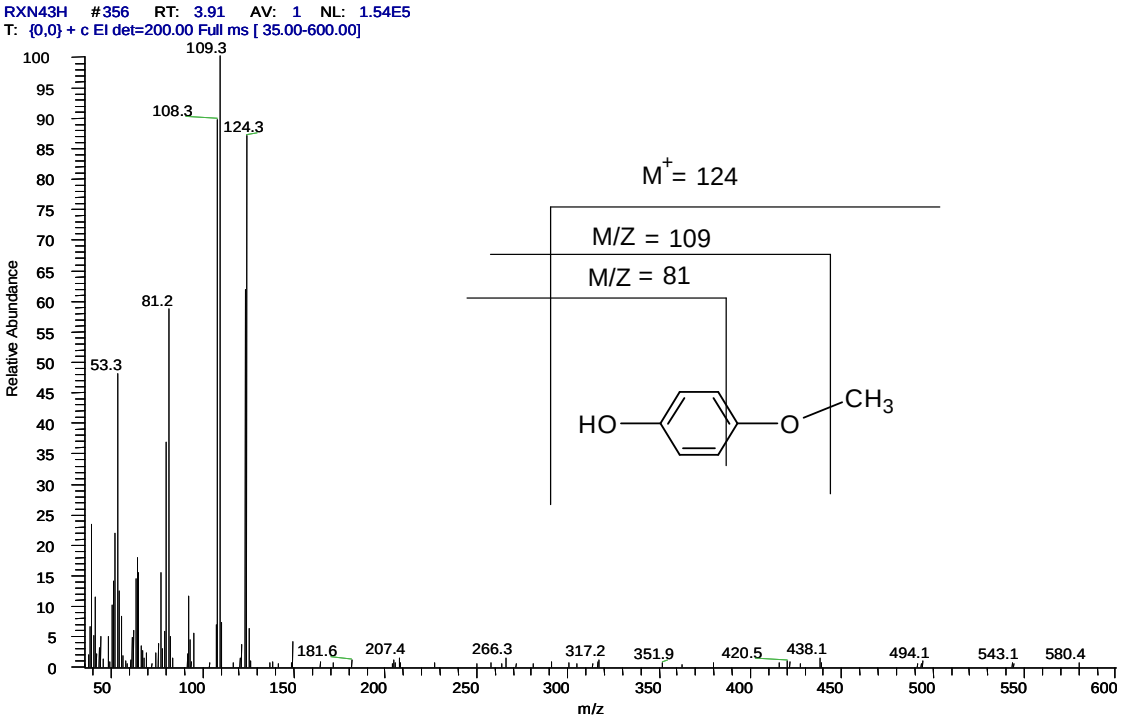


**Figure 2.89: Mass fragmentation pattern: Peak No. 4**

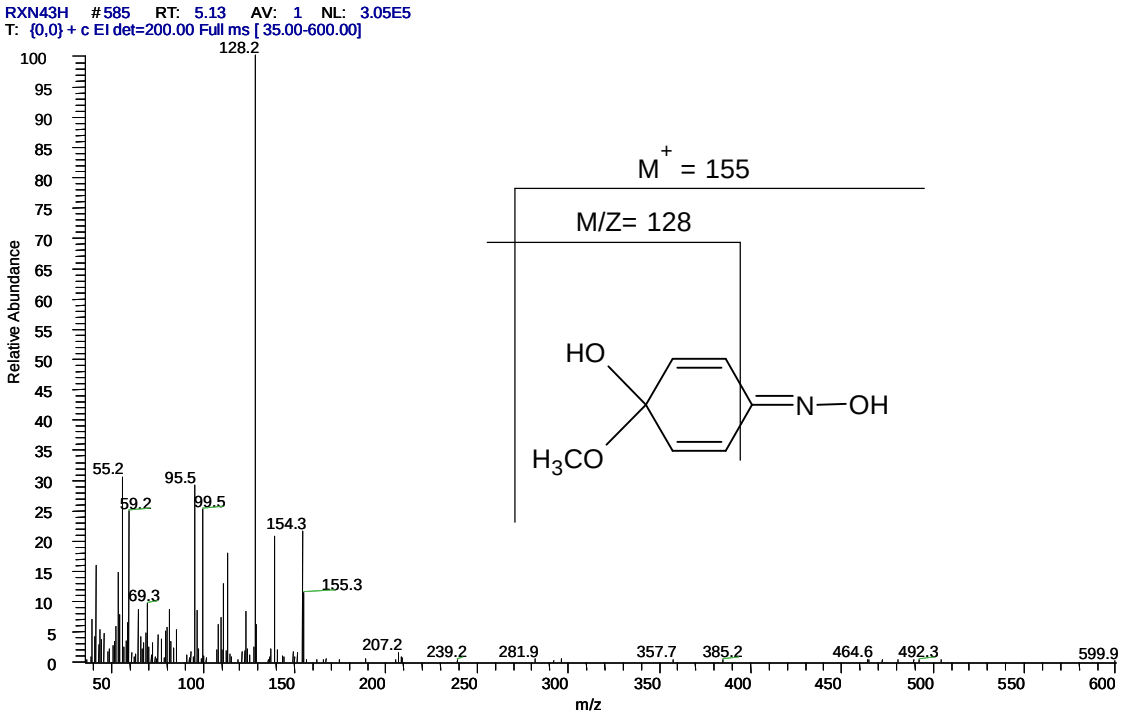



**Figure 2.90: Mass fragmentation pattern: Peak No. 5**

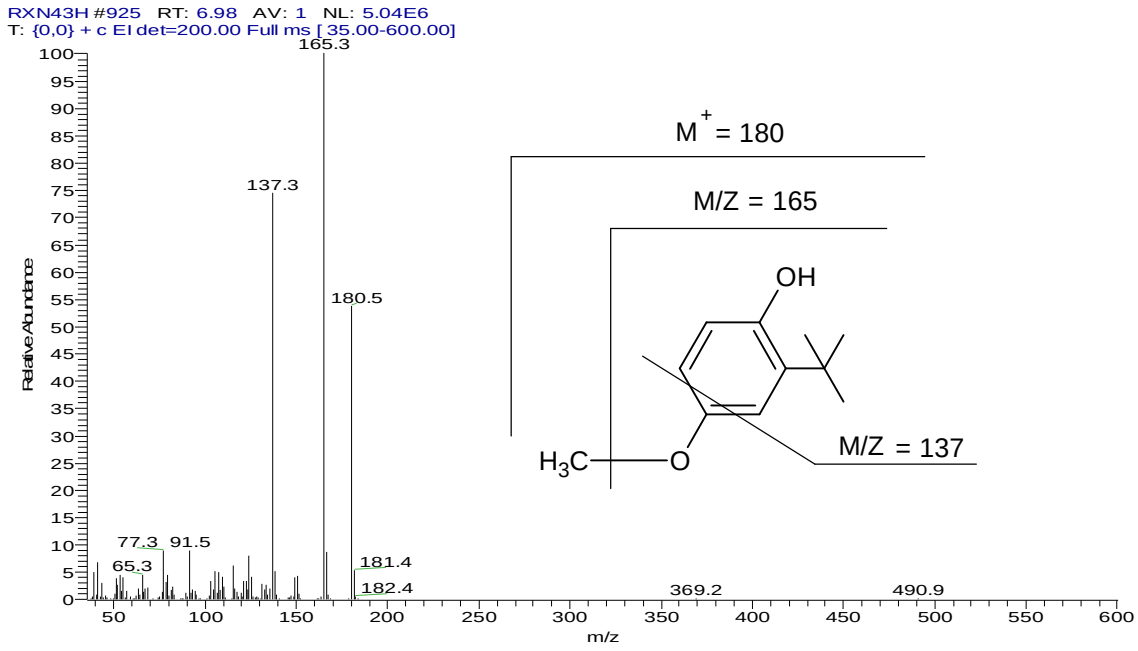


**Figure 2.91: Mass fragmentation pattern: Peak No. 6**

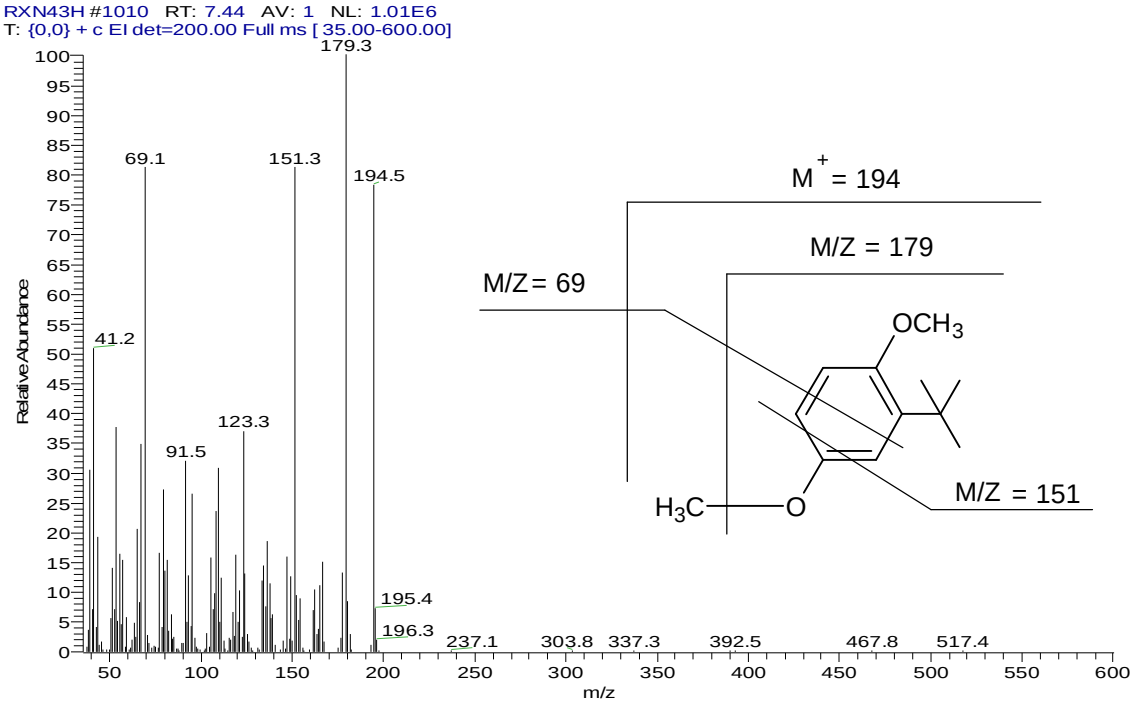



**Figure 2.92: Mass fragmentation pattern: Peak No. 7**

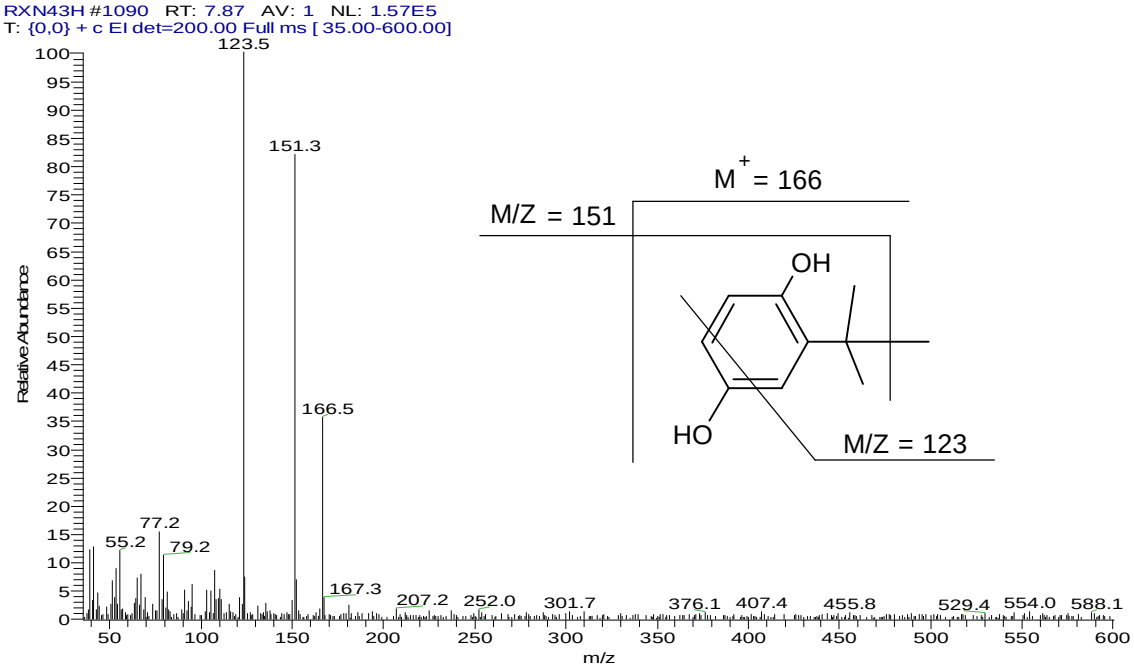
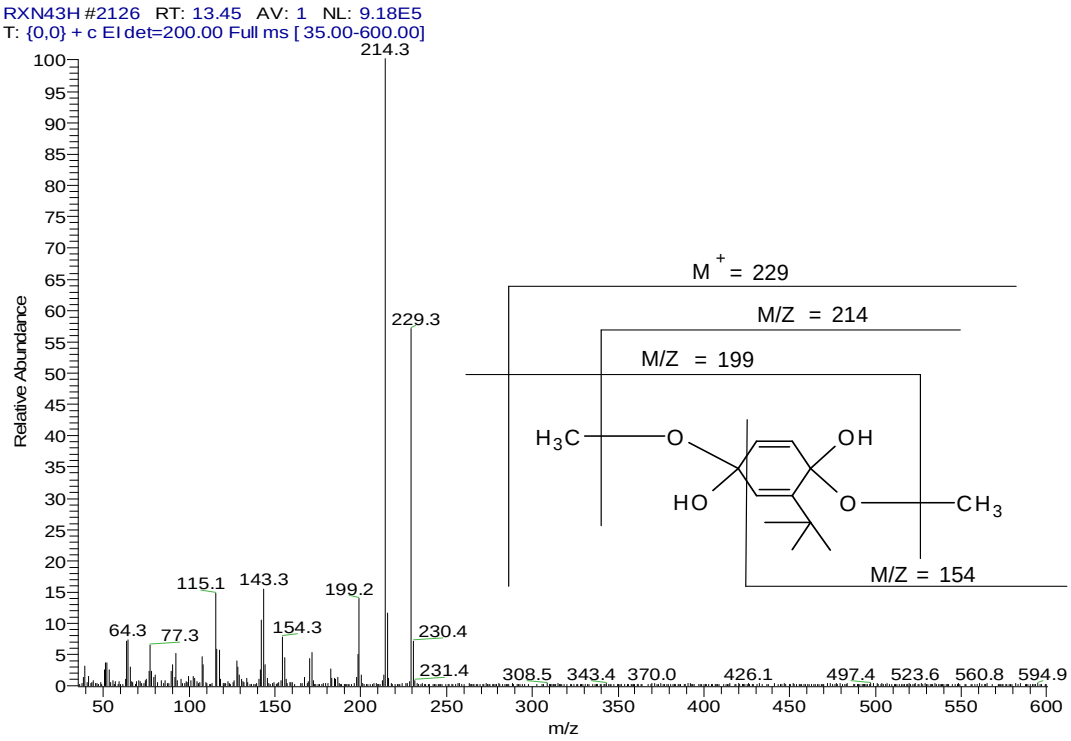
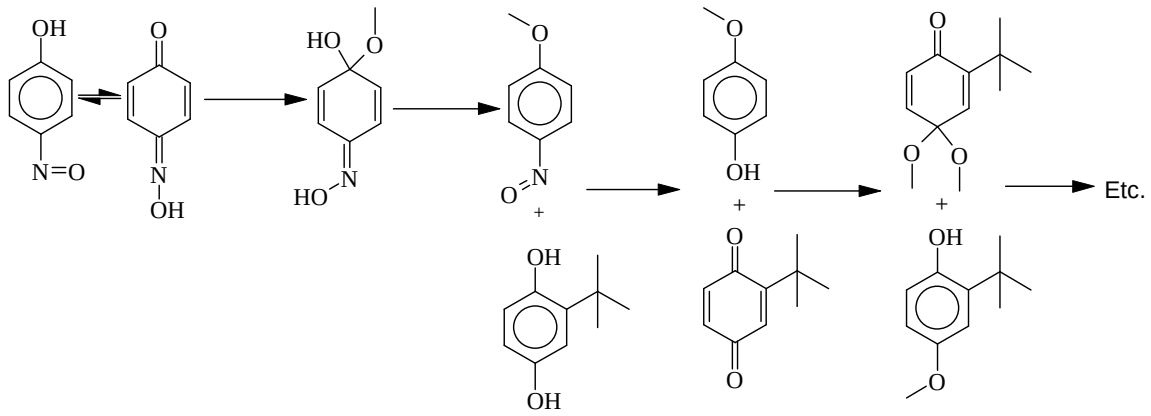


**Figure 2.93: Mass fragmentation pattern: Peak No. 8**



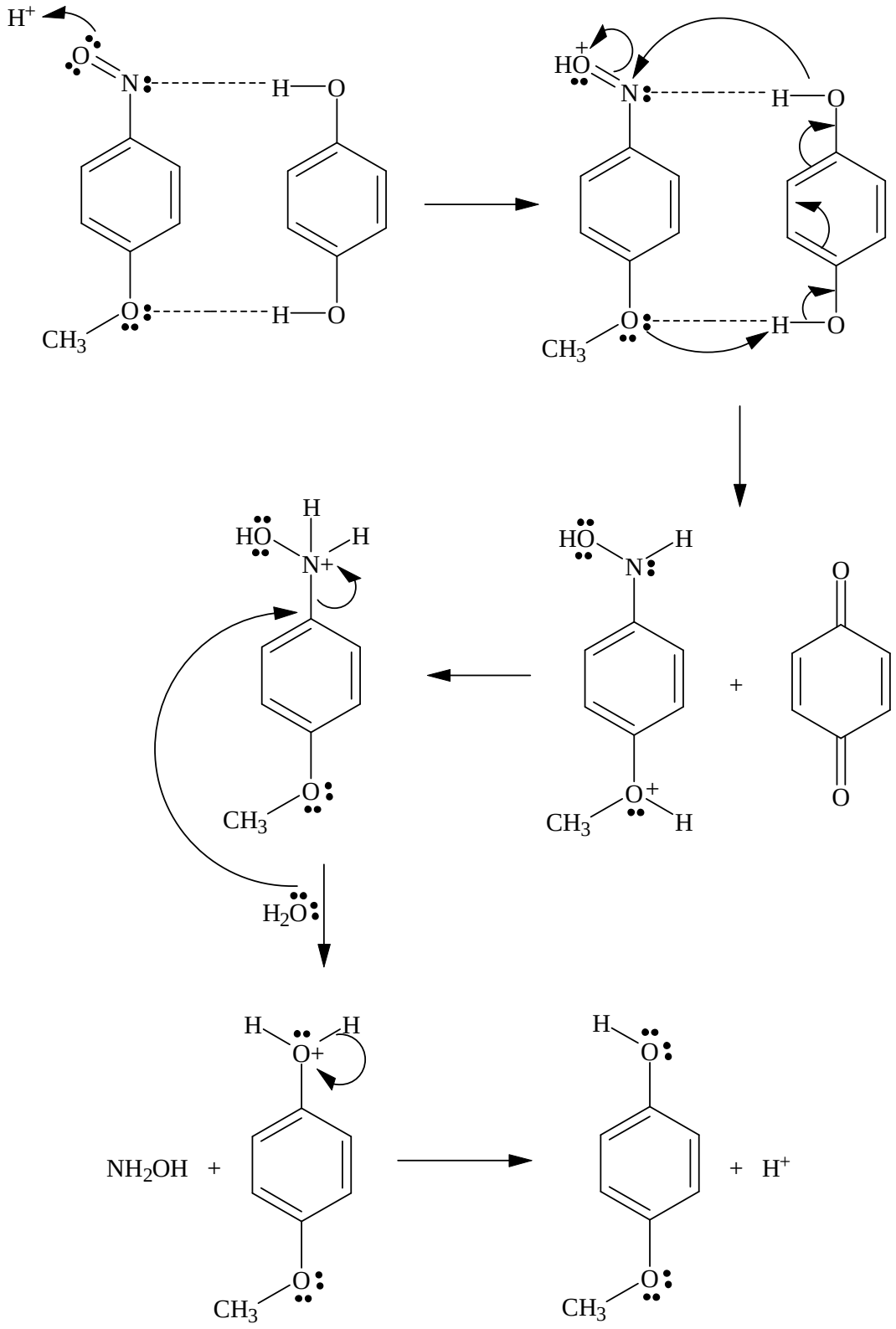

The cross-over reaction between 4-nitrosophenol and 2-*tert*-butylhydroquinone produces the intermediates and products illustrated in Scheme 33.




**Scheme-33: Cross-over reaction between 4-nitrosophenol and 2-*tert*-butylhydroquinone**

The formation of 1-methoxy-4-(hydroxyimino)cyclohexa-2,5-dien-1-ol suggests that the pathway to the formation of 4-methoxyphenol from 4-nitrosophenol is probably somewhat different to that of the hydroquinone:benzoquinone reaction. The first primary product in the reaction is therefore 1-methoxy-4-nitrosobenzene (4-nitrosoanisole), and the results described above clearly indicate that the formation of a pi-bonded complex with either hydroquinone or benzoquinone is not required for this reaction to proceed.

The conversion of 4-nitrosoanisole into 4-methoxyphenol, however, probably requires the formation of such a pi-bonded complex since no 4-methoxyphenol is formed in the absence of hydroquinone (or benzoquinone). The conversion of 4-nitrosoanisole into 4-methoxyphenol in the presence of hydroquinone is therefore proposed to proceed as shown in Scheme 34.



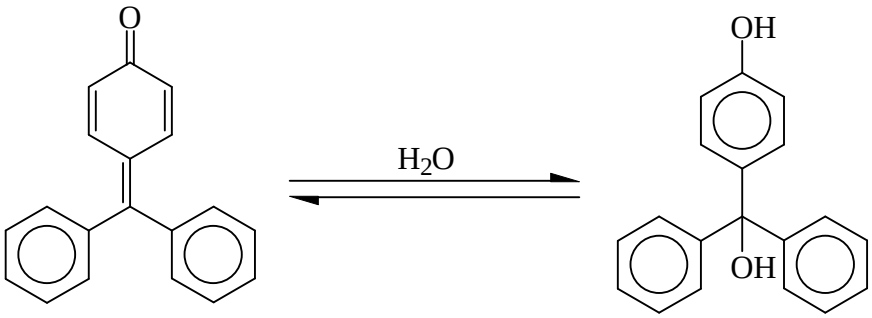
**Scheme-34: Conversion of 4-nitrosoanisole into 4-methoxyphenol**

The other products observed during the above cross-over reactions can be explained in terms of the considerations given previously for the cross-over reaction between 2-*tert*- butylhydroquinone and benzoquinone as they result only from the 2-*tert*-butylhydroquinone portion of the reaction mixture.

## 2.5 Reaction of methanol with benzoquinone or hydroquinone in the presence of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one

### 2.5.1 Introduction

*p*-Quinone methides, also known as fuchsones, are highly conjugated cyclic enones that exhibit interesting physico-chemical properties. Such compounds have been the subject of many NMR, UV/Vis and theoretical studies.[2-5] In view of their ability to undergo hydration/dehydration equilibria to form either the quinone methide or carbinol structure, it was of interest to investigate the potential interaction between 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and hydroquinone (or its hydrated form, (4-hydroxyphenyl)diphenylmethan-1-ol, with benzoquinone) when hydroquinone (or benzoquinone) is reacted with an alcohol in the presence of an acid catalyst.




### 2.5.2 Reaction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one with methanol

It has been shown earlier (Sections 2.2.8 and 2.2.9) that when mixtures of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and either hydroquinone or

benzoquinone were reacted with methanol in the absence of an acid catalyst, no reaction was observed. However, when 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one was reacted with methanol in the presence of an acid catalyst, a substantial amount of 1-(diphenylmethyl)-4-methoxybenzene may be observed in the GC-traces of reaction mixtures. Figures 2.94 and 2.95 show the GC-MS traces for the sample of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one before reaction and one hour after reaction with methanol in the presence of sulphuric acid as catalyst.

**Figure 2.94: GC-MS trace of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one before reaction**

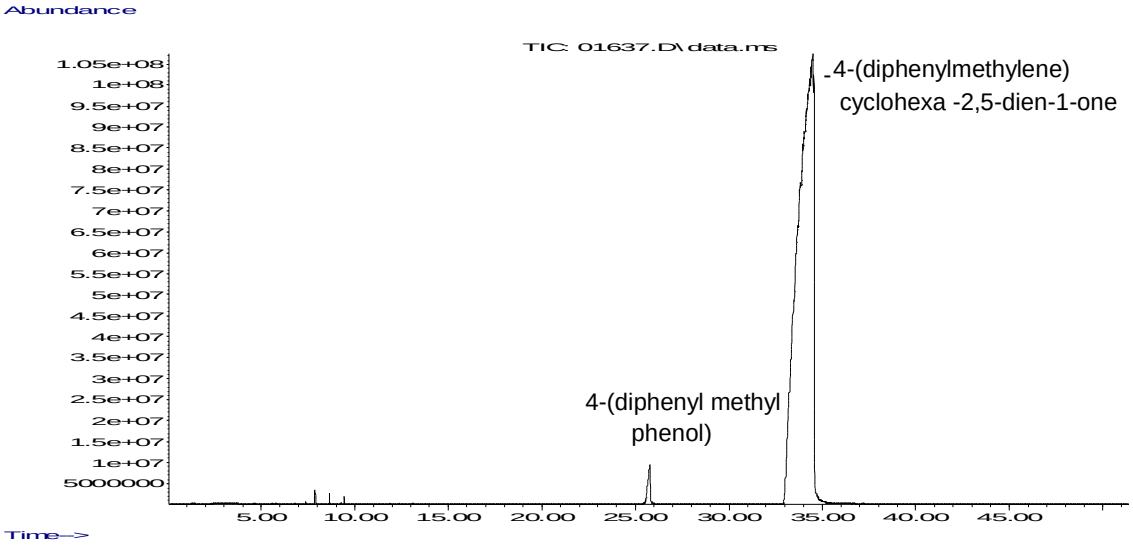


**Figure 2.95: GC-MS trace of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one reaction with methanol and catalyst after 1 hour**

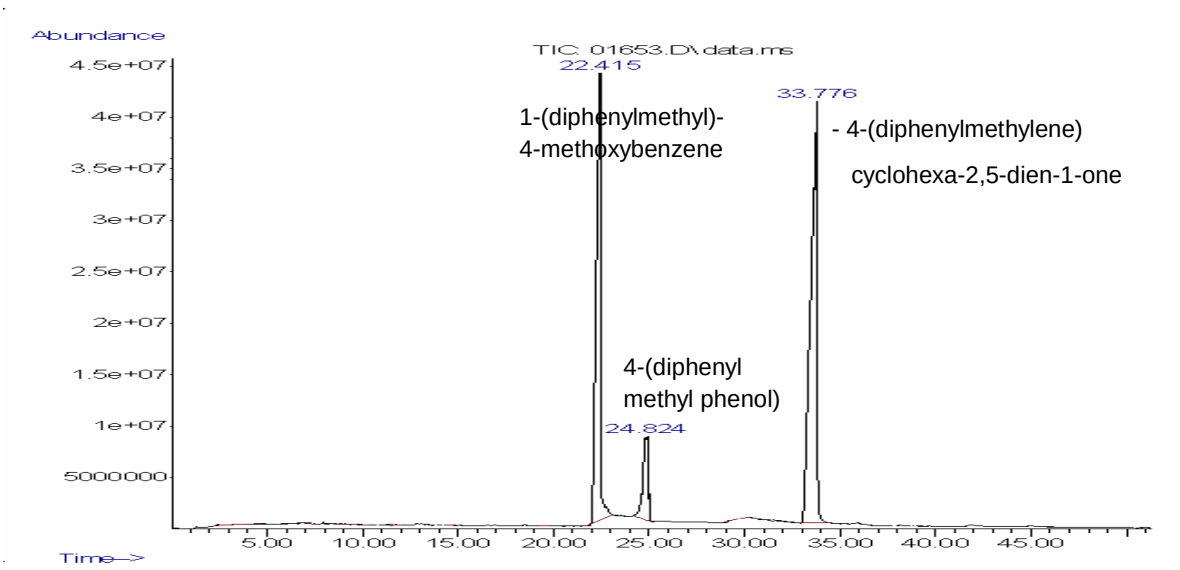
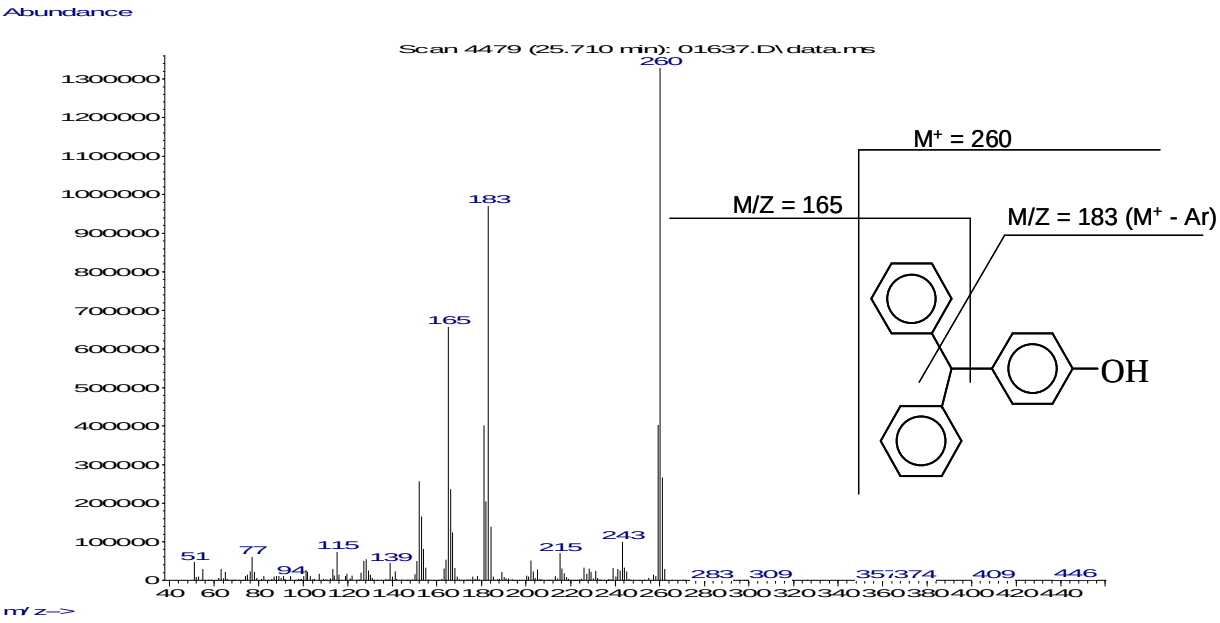
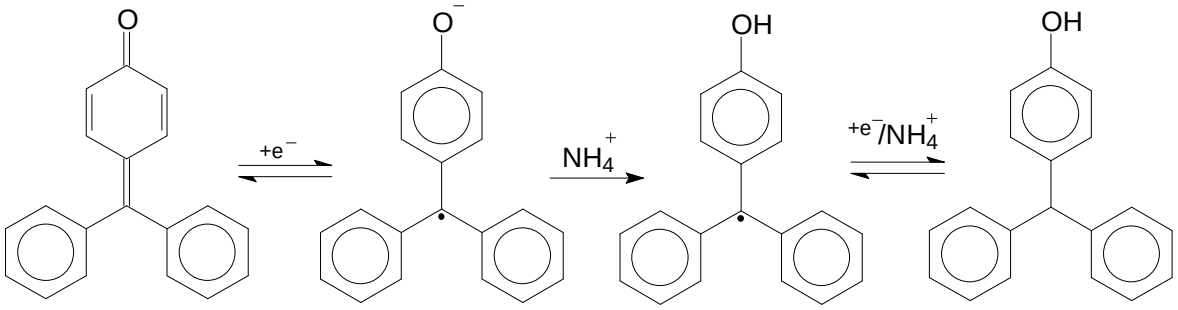



Figure 2.94 shows that the fresh 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one sample contains a small amount of impurity (peak at 26.7 min.). The fragmentation pattern of this impurity corresponds to a structure consistent with that of 4-(diphenylmethyl)phenol as illustrated in Figure 2.96.

**Figure 2.96: Mass fragmentation pattern for (diphenylmethyl)phenol**



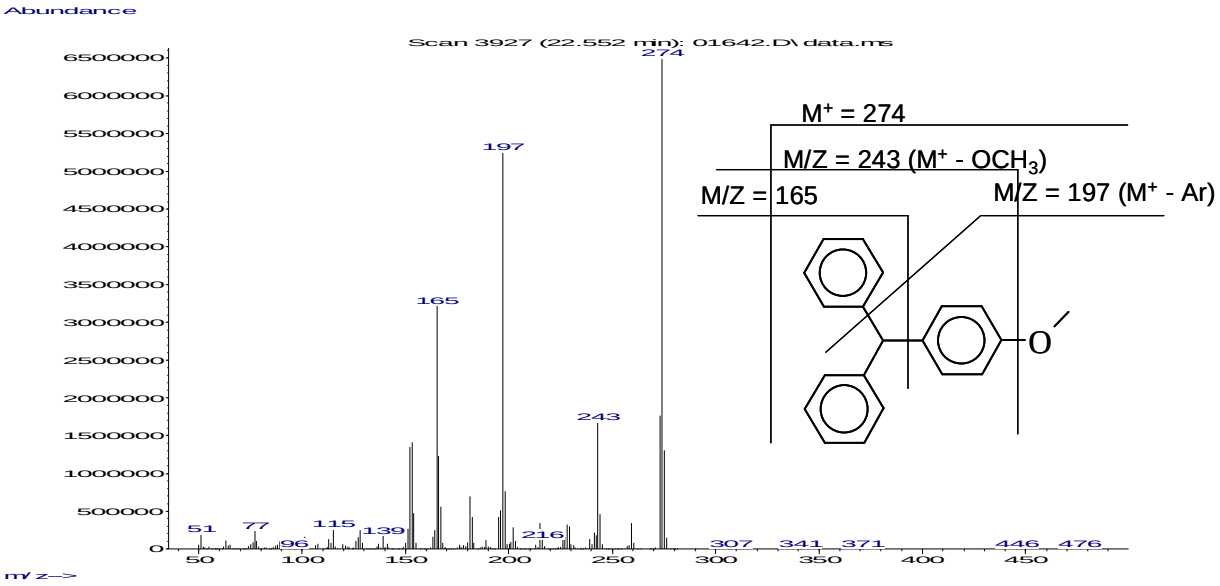
This impurity, which corresponds to a reduced form of the product 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one is most probably by reaction with the Grignard reagent used to synthesize the 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one via a single electron transfer process. Quinone methides are known to form relatively stable radical anions.[79] Scheme 35 depicts a possible radical-anion mechanism for this reduction.



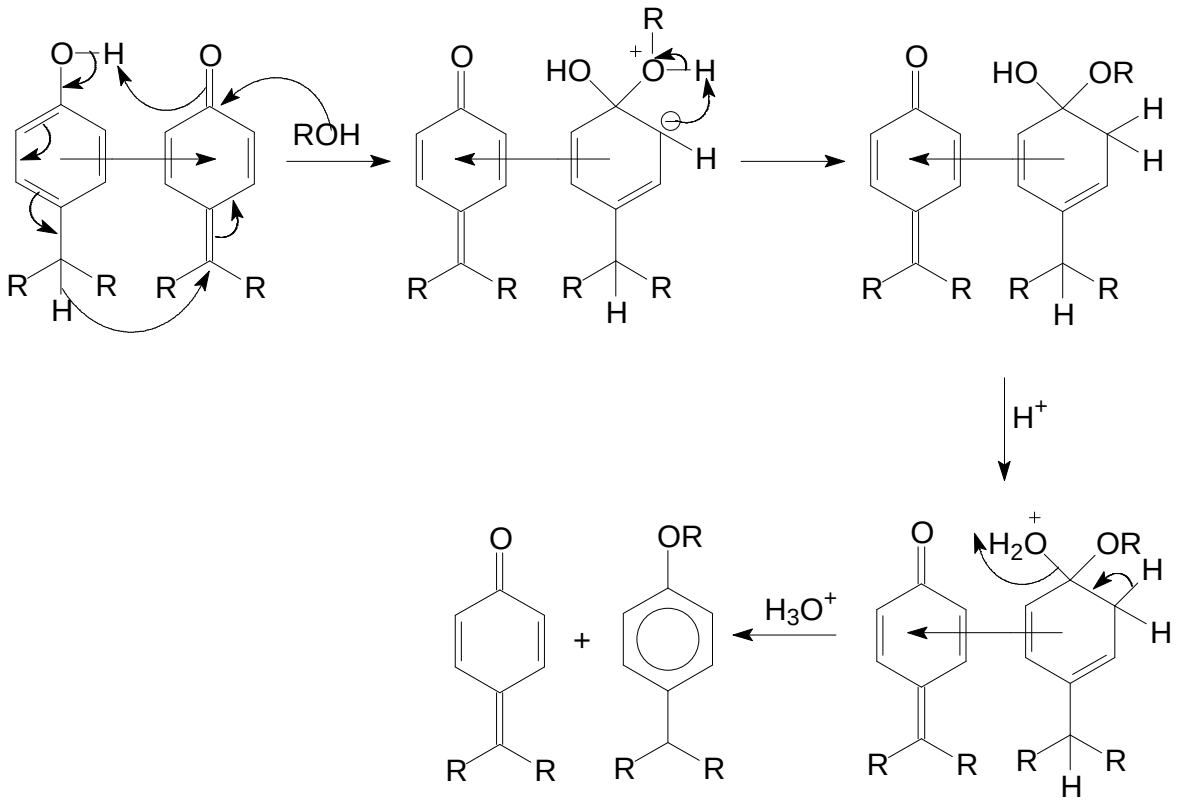

**Scheme-35: Reduction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one**

From Figure 2.94 (after 1 hour of reaction with methanol in the presence of sulphuric acid), a new product has been formed (peak at 22.4 minutes). The fragmentation pattern of this compound is consistent with that of 1-(diphenylmethyl)-4-methoxybenzene as illustrated in Figure 2.96.

**Figure 2.97: Mass fragmentation pattern for 1-(diphenylmethyl)-4-methoxybenzene**




From the relative intensities of the GC-MS peaks in Figures 2.94 and 2.95, it is clear that the 1-(diphenylmethyl)-4-methoxybenzene must have been formed from 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one as the relative intensity of the 4-(diphenylmethyl)phenol peak remains virtually unchanged. A possible explanation for the formation of 1-(diphenylmethyl)-4-methoxybenzene from 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one is illustrated in Scheme 36. The proposed pathway invokes the formation of a pi-bonded complex between 4-(diphenylmethyl)phenol and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one in a manner analogous to that between hydroquinone and benzoquinone. Under conditions of acid catalysis, nucleophilic attack by the alcohol and subsequent reduction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one by 4-(diphenylmethyl)phenol leads to the observed product in a manner analogous to that proposed for the formation of 4-methoxyphenol from a hydroquinone/benzoquinone complex (Scheme 29).




**Scheme 36: Proposed mechanism for the formation of 1-(diphenylmethyl)-4-methoxybenzene**

### 2.5.3 Reaction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone mixtures with methanol

In order to establish whether benzoquinone and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one mixtures will facilitate the reaction of either the benzoquinone or the 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one with methanol in the presence of sulphuric acid as the acid catalyst, equimolar amounts of benzoquinone and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one were reacted with methanol as before. During these reactions, the amount of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone used was 0.40 mmol respectively, while the amount of acid catalyst (0.051g; 0.519 mmol) and the amount of methanol (20 mL) were as before. Reactions were carried out at a reaction temperature of 64 $^{0}$C.

Reaction products formed during these reactions were identified from the mass fragmentation patterns of the individual products as observed in the GC-MS traces of reaction mixtures, as well as by comparing mass fragmentation patterns to those of standard reference compounds. Figure 2.97 shows a typical GC-MS trace for a reaction mixture when an equimolar mixture of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone is reacted with methanol in the presence of sulphuric acid as catalyst. The mass fragmentation patterns for the peaks numbered 1 - 4 in Figure 2.98 are shown in Figures 2.99 to 2.102, together with the assignments made for each component. Peaks 5, 6, and 7 in the chromatogram have the same assignments shown above for the reaction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one with methanol (Figure 2.95).

**Figure 2.98: GC-MS chromatogram (4-(diphenylmethylene)cyclohexa-2,5-dien-1-one + benzoquinone): Reaction time = 1 hour**

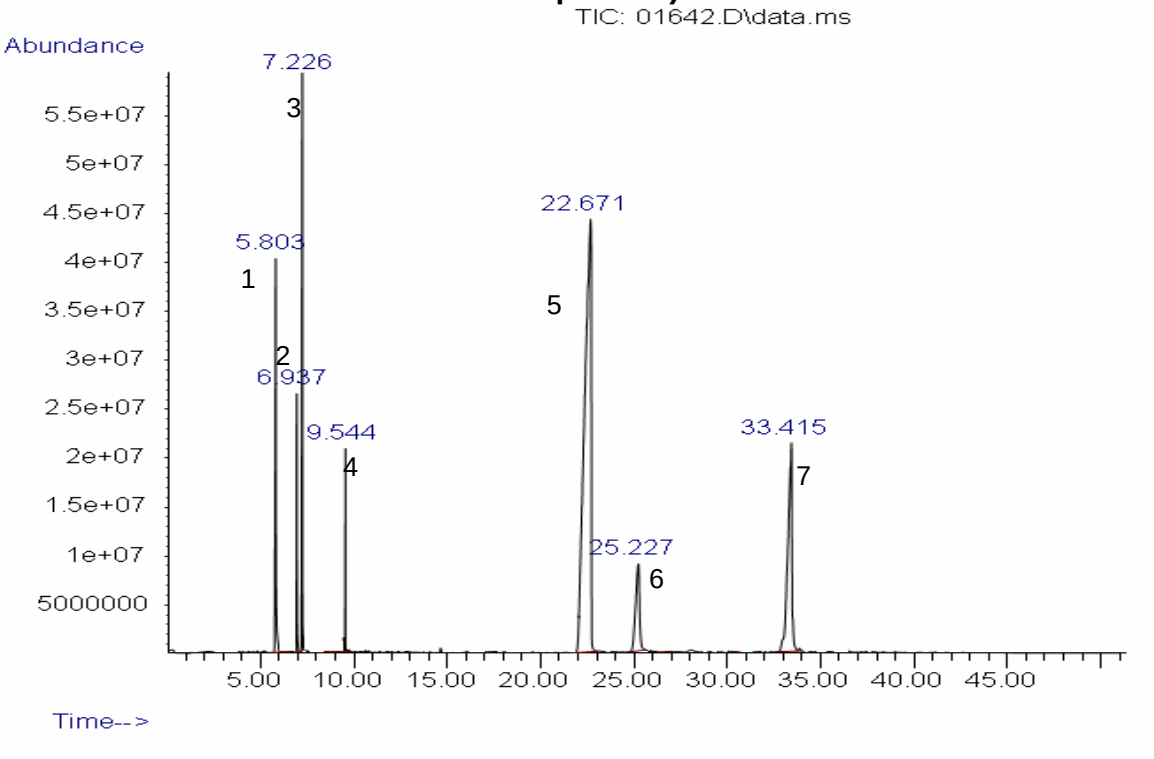


**Figure 2.99: Mass fragmentation pattern: Peak No. 1**

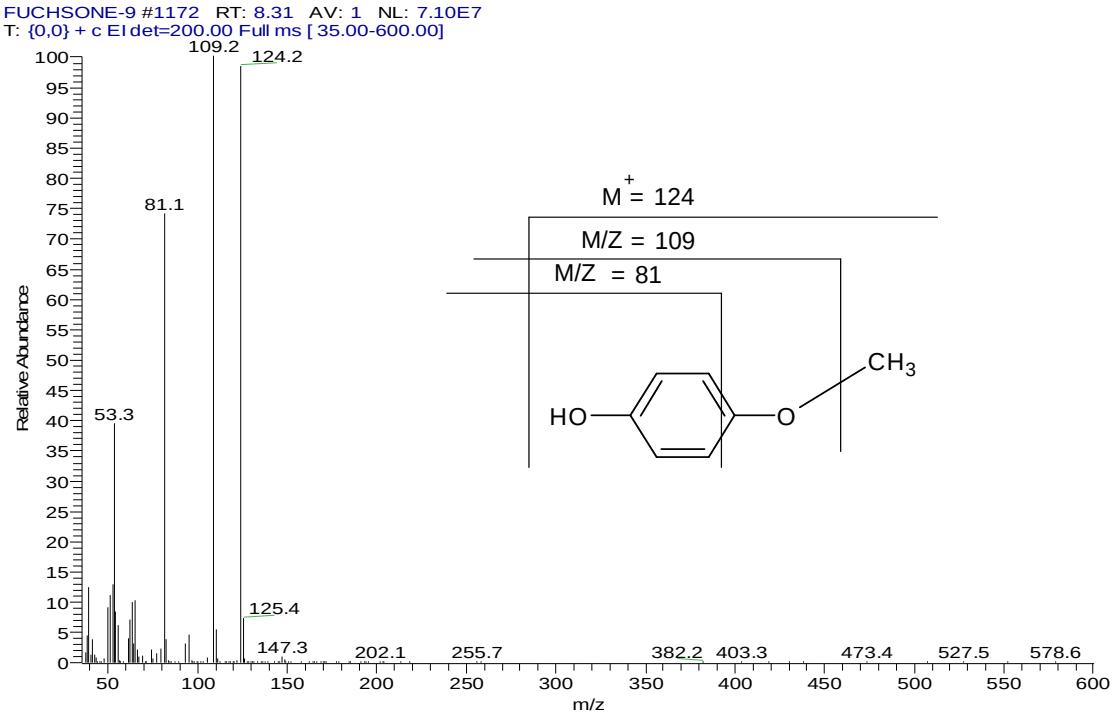



**Figure 2.100: Mass fragmentation pattern: Peak No. 2**

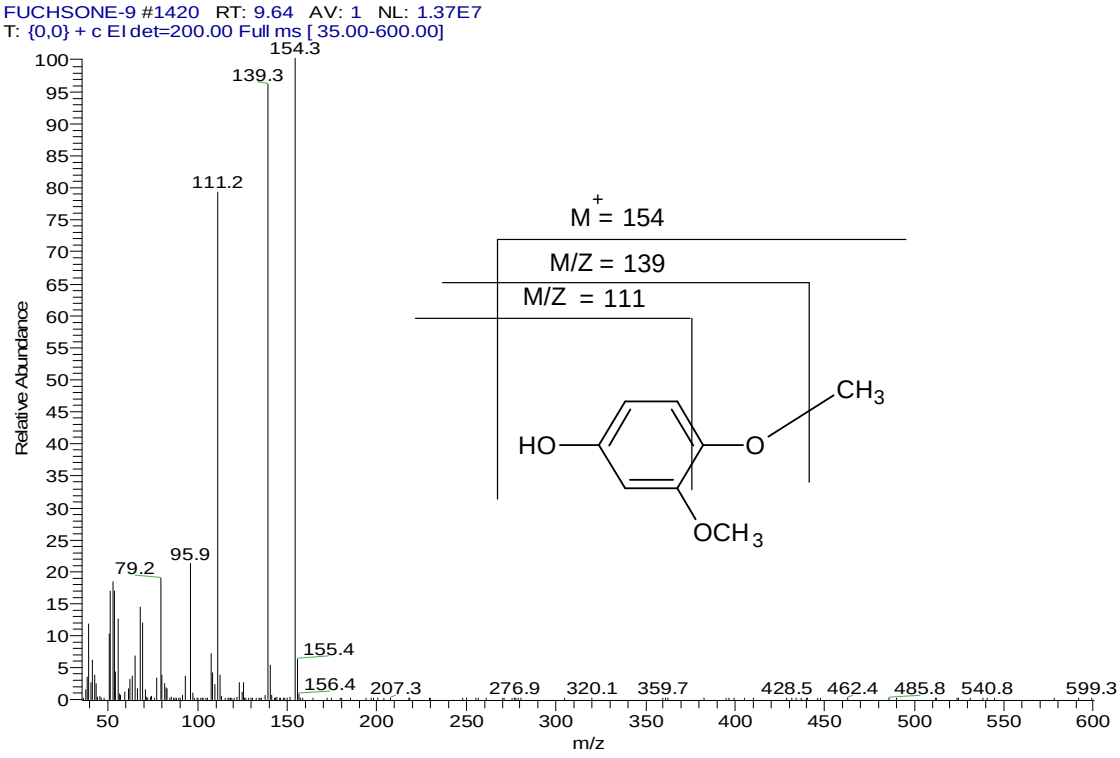


**Figure 2.101: Mass fragmentation pattern: Peak No. 3**

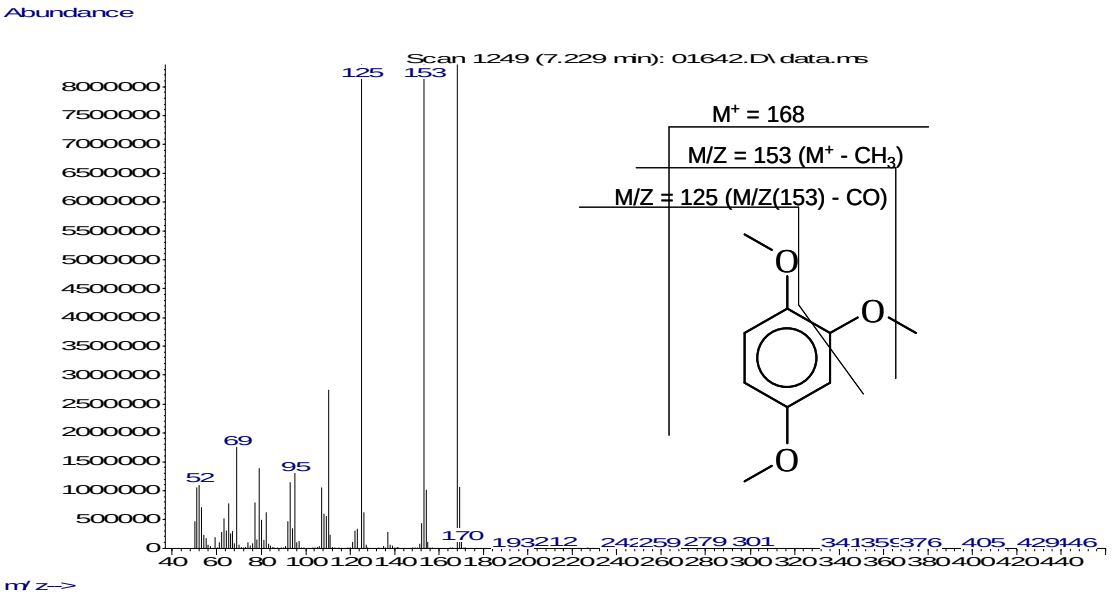
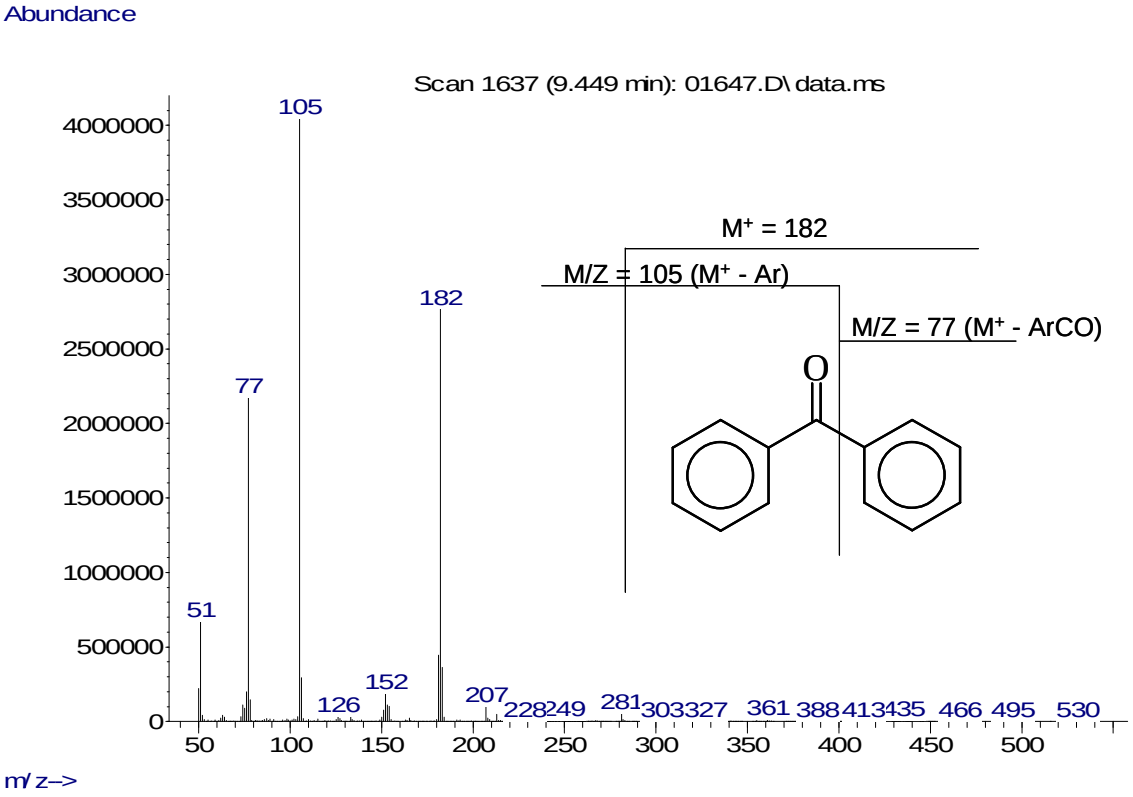
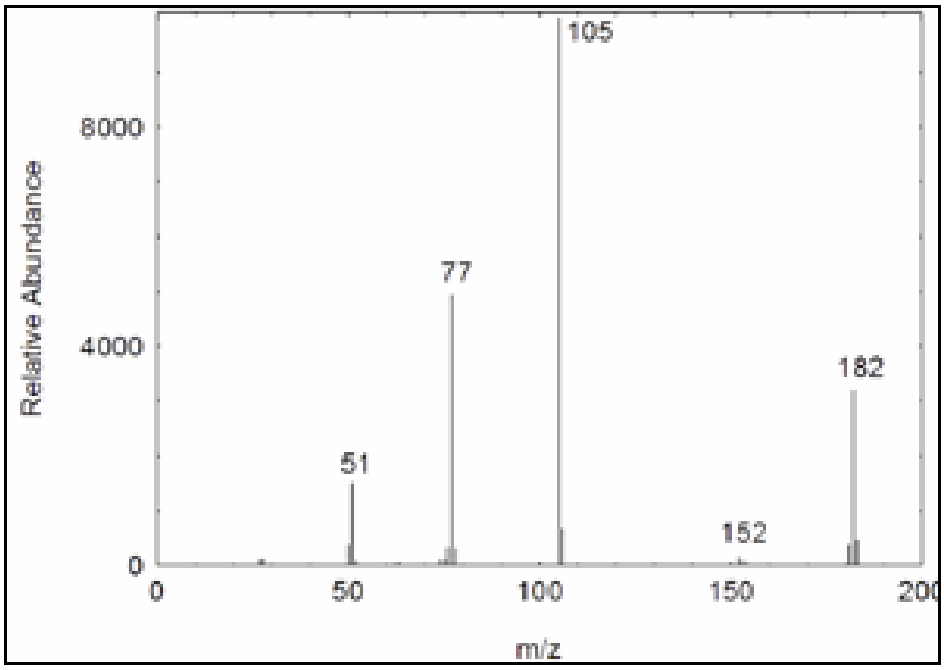



**Figure 2.102: Mass fragmentation pattern: Peak No. 4**



The last assignment (Peak No. 4) was confirmed by comparing the experimentally obtained mass fragmentation pattern to a reference mass fragmentation pattern for this compound (Figure 2.103).[73]

**Figure 2.103: Mass fragmentation pattern for benzophenone: NIST**



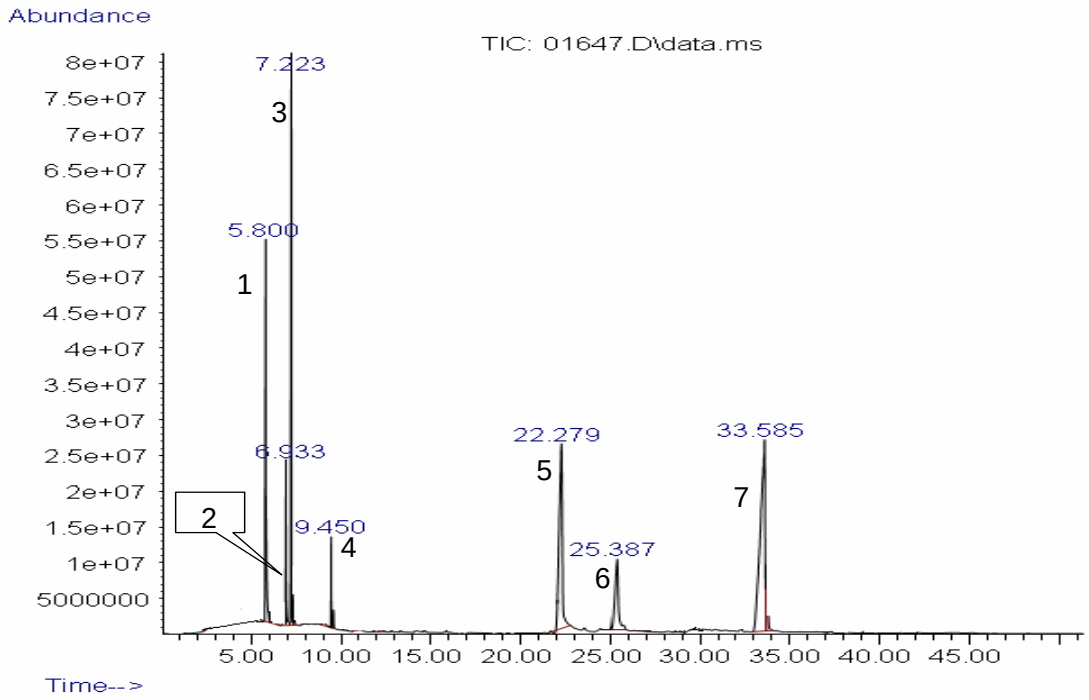

Before discussing the above results for the reaction of an equimolar mixture of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone with methanol in the presence of an acid catalyst, the results for the equivalent reaction when using an equimolar mixture of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and hydroquinone will first be presented.

### 2.5.4 Reaction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and hydroquinone mixtures with methanol

The reaction as described above for equimolar mixtures of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone was repeated exactly, but replacing the benzoquinone with hydroquinone. Figure 2.104 illustrates

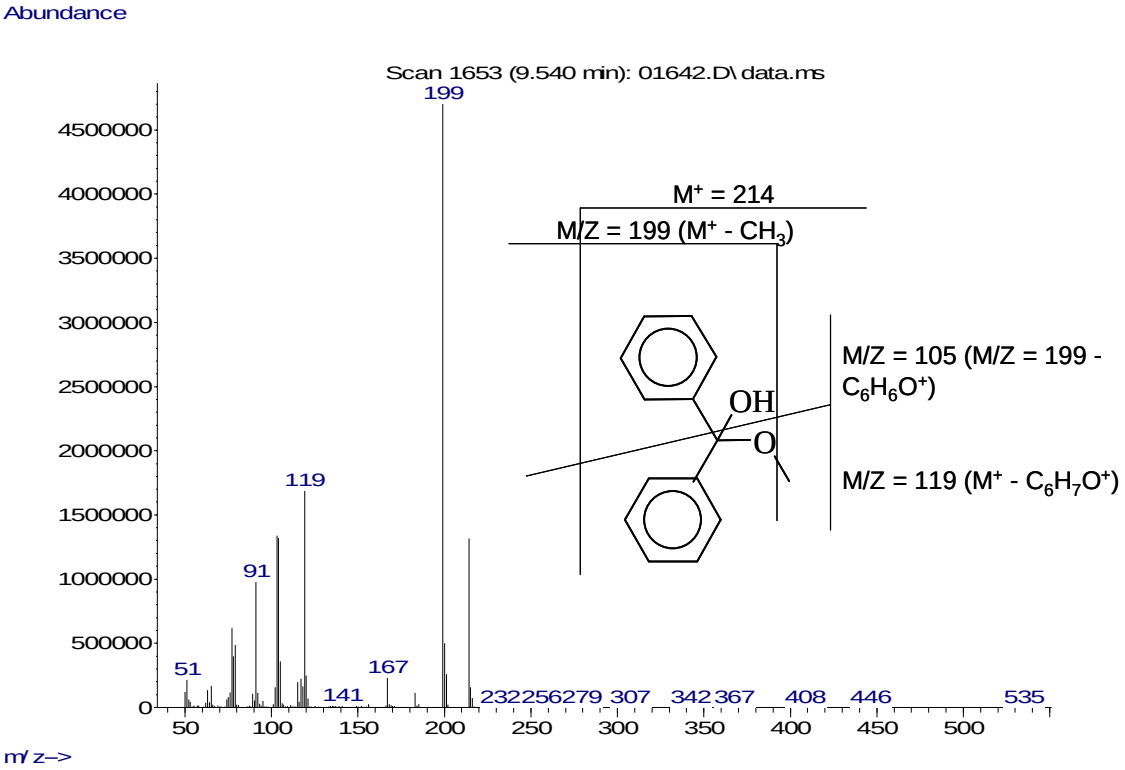
a typical GC-MS chromatogram for reaction mixtures obtained during these reactions.

**Figure 2.104: GC-MS chromatogram (4-(diphenylmethylene)cyclohexa-2,5-dien-1-one + hydroquinone): Reaction time = 1 hour**




The peaks numbered 1,2,3 and 5,6, and 7 have the same assignments as those made for the 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone reaction (Figure 2.98). The mass fragmentation pattern for peak 4 in the above chromatogram (Figure 2.104) is consistent with the structure of methoxydiphenylmethan-1-ol as shown in Figure 2.105.

**Figure 2.105: Mass fragmentation pattern: Peak 4**



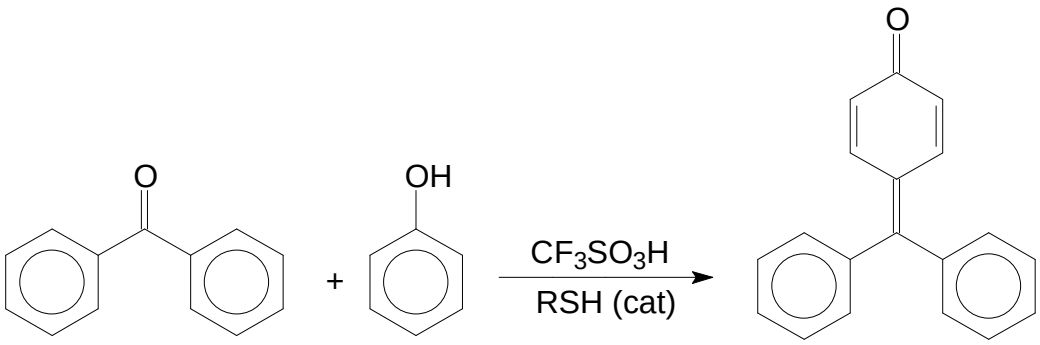

### 2.5.5 Discussion: Reaction of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone/hydroquinone mixtures with methanol

The results obtained for the reaction of equimolar quantities of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone (or hydroquinone) mixtures with methanol in the presence of sulphuric acid as catalyst suggests that a number of interactions between the reaction components may be influencing the outcome of the reaction. These potential interactions are as follows:

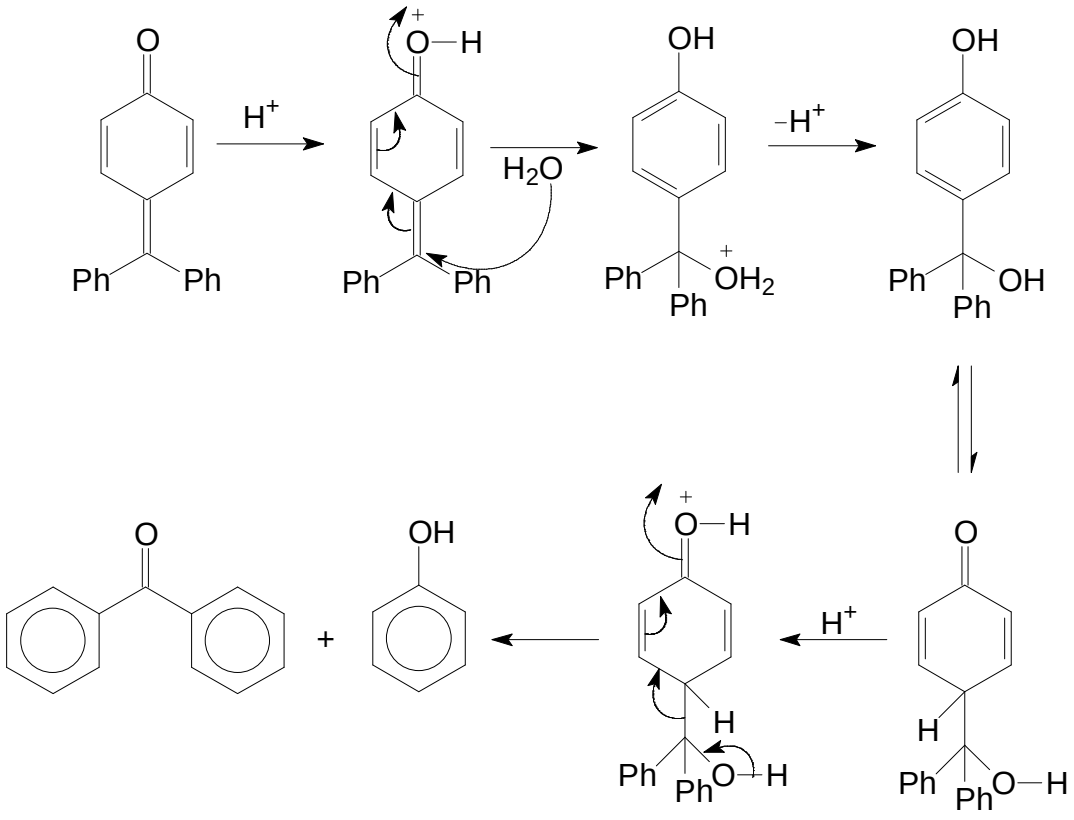
- The interaction between 4-(diphenylmethyl)phenol and 4-(diphenylmethylene) cyclohexa-2,5-dien-1-one. This particular interaction has already been discussed in Section 2.4.1. This interaction facilitates the formation of 1-(diphenylmethyl)-4-methoxybenzene as discussed previously.

- The interaction between benzoquinone and 4-(diphenylmethyl)phenol. In the absence of any detectable 4-(hydroxyphenyl)diphenylmethan-1-ol it seems reasonable to invoke this particular interaction in order to explain the formation of the observed reaction products, 4-methoxyphenol, 3,4-dimethoxyphenol, and 1,2,4-trimethoxybenzene from the initially added benzoquinone in a manner analogous to that discussed previously for the formation of these compounds from hydroquinone/benzoquinone mixtures (Section 2.3), as well as the formation of 1-(diphenylmethyl)-4-methoxybenzene from the reaction of 4-(diphenylmethyl)phenol and 4-(diphenylmethylene) cyclohexa-2,5-dien-1-one mixtures with methanol (Section 2.4.1).

  In addition to the products referred to above, the GC-MS traces of reaction mixtures of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone contains an additional major product, namely benzophenone. Since it is known that the condensation reaction between benzophenone and phenol in the presence of strong acid catalysts (Scheme 37) may be enhanced by the azeotropic removal of water,[80] it is tempting to propose the formation of benzophenone via the hydrolysis of 4-(diphenylmethylene) cyclohexa-2,5-dien-1-one (Scheme 38).




**Scheme-37: Condensation of phenol and benzophenone**

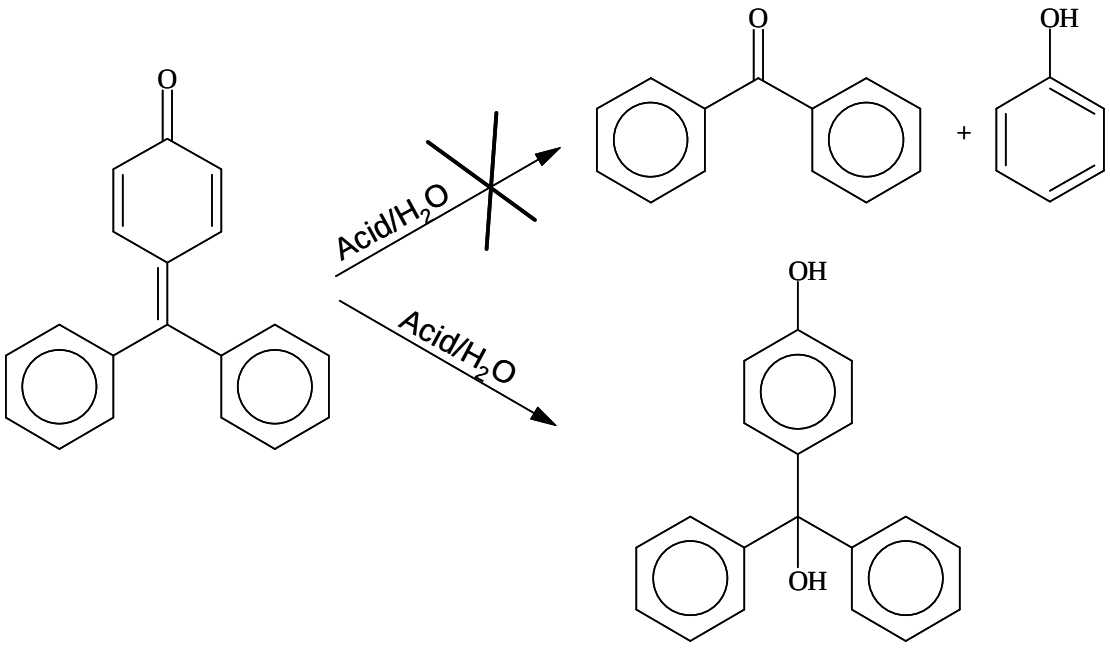


**Scheme-38: Hydrolysis of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one**

While the formation of the observed benzophenone via a hydrolysis pathway as illustrated above cannot be entirely excluded, two observations mitigate against such a route. These are:

- The fact that phenol is not observed as co-product during these reactions, and;
- The observation that in reactions where hydroquinone is used in place of benzoquinone, no benzophenone is detected. Instead, hydroquinone and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one mixtures result in the formation of methoxydiphenylmethan-1-ol (Figure 105).

In addition to the above, it has been reported[80] that the hydrolysis of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one results in the formation of (4-hydroxyphenyl)diphenylmethan-1-ol as shown in Scheme 39.




**Scheme-39: Reported hydrolysis of (4-hydroxyphenyl)diphenylmethan-1-ol**

The above observations strongly suggest that the observed reaction products do not result from “simple” hydrolysis reactions and must involve the participation of the added benzoquinone (or hydroquinone). In view of the fact that it was not possible during this investigation to unequivocally determine which other products form as a result of the benzoquinone-formation reaction, it is quite difficult to propose a possible pathway for the formation of benzophenone during these reactions.

- The interaction between hydroquinone and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one. This particular reaction has already been referred to above and most probably results in the formation of the observed product, methoxydiphenylmethan-1-ol (Figure 105). As in the case of the benzoquinone and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one mixtures, it is quite difficult to envisage a possible pathway for the formation of this product in the absence of a full knowledge regarding which other product (or products) are formed during this particular reaction.

## 2.6 Summary and concluding remarks

The results obtained during this investigation have clearly shown that the existence of pi-bonding between certain aromatic systems containing a phenolic group attached to the aromatic ring and a quinone system can result in the activation of one or both systems for nucleophilic substitution reactions under conditions of acid catalysis.

In the case of the hydroquinone/benzoquinone system, this pi-interaction results in the highly selective formation of 4-methoxyphenol from both the hydroquinone and benzoquinone. This is thought to be the result of the inter-conversion of benzoquinone to hydroquinone (and vice versa) during these reactions.

In the case of 4-nitrosophenol and hydroquinone (or benzoquinone) systems, the normal reaction product, 4-nitrosoanisole resulting from the reaction of methanol with 4-nitrosophenol under acid catalysis, is reduced significantly when either hydroquinone or benzoquinone is added. In the latter case, 4-methoxyphenol is observed as an additional reaction product.

The results from the investigation of the interaction between mixtures of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and hydroquinone or benzoquinone are somewhat less clear than in the previous two cases. The formation of products such as benzophenone [in mixtures of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and benzoquinone] and methoxydiphenylmethan-1-ol [in mixtures of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one and hydroquinone], however, strongly suggests the existence of similar interactions since it would be very difficult to rationalize the formation of these products otherwise.

Cross-over reactions between an unsubstituted hydroquinone (or benzoquinone) and a substituted benzoquinone (or hydroquinone) was used to gain further insight into the mechanistic pathway involved during these reactions. The results of these cross-over reactions were used to propose a mechanistic pathway that could

explain the requirement for pi-interaction between the hydroquinone and benzoquinone molecules, the role of the acid catalyst, as well as the relative rates of hydroquinone and benzoquinone consumption during these reactions. The mechanism was also capable of explaining all the reaction products observed during these reactions.

In conclusion, the exploitation of pi-interactions between molecules of the types investigated during this work opens an interesting field of chemistry. Clearly, the level of understanding developed during this work is only beginning to address this interesting field of chemistry and much work will need to be done to gain a fuller understanding of the chemistry involved as well as the potential synthetic value of these interactions.

# CHAPTER 3

## EXPERIMENTAL

## 3.1 Materials

### 3.1.1 Reagents for synthesis

The reagents used during the reactions, together with their supplier and respective grades, are listed in Tables 3.1 and 3.2.

**Table 3.1: Organic reagents for synthesis**

| Chemical | Formula | Supplier | Grade/Purity |
|---|---|---|---|
| Acetic anhydride | $C_4H_6O_3$ | Aldrich | 99.50% |
| Amberlite IR-120 (plus) | -- | Aldrich | -- |
| Bromobenzene | $C_6H_5Br$ | Aldrich | 99+% |
| n-Butanol | $C_4H_{10}O$ | Saarchem | 99% |
| 1,4-Benzoquinone | $C_6H_4O_2$ | Aldrich | 98% |
| 2-*tert*-Butyl, 1,4-benzoquinone | $C_{10}H_{12}O_2$ | Aldrich | 98% |
| Dichloromethane | $CH_2Cl_2$ | Merck | 99% (GC) |
| Diethyl ether | $(CH_3CH_2)_2O$ | Merck | 99% (GC) |
| Ethanol | $C_2H_5OH$ | Merck | 99.5% (GC) |
| Ethyl acetate | $C_2H_6O$ | Saarchem | AR |
| Ethylene glycol | $HO(CH_2)_2OH$ | Saarchem | -- |
| Hydroquinone | $C_6H_6O_2$ | Aldrich | 99+% |
| 2-*tert*-Butyl hydroquinone | $C_{10}H_{14}O_2$ | Aldrich | 97% |
| Methanol | $CH_3OH$ | Merck | AR, 99.5% |
| Methyl, 4-hydroxybenzoate | $C_8H_8O_3$ | Merck | 99% (GC) |

**Table 3.1: Organic reagents for synthesis continued …..**

| | | | |
|---|---|---|---|
| Phenol | $C_6H_5OH$ | Saarchem | UNIV-AR, min 99.5% |
| Petroleum ether ($30^0C$ – $60^0C$) | -- | Saarchem | UNIV-AR |
| Terahydrofuran | $C_4H_8O$ | Saarchem | UNI-LAB, min 98% |

**Table 3.2: Inorganic reagents for synthesis**

| **Chemical** | **Formula** | **Supplier** | **Grade/Purity** |
|---|---|---|---|
| Ammonium chloride | $NH_4Cl$ | Saarchem | 99% |
| Deionized water | $H_2O$ | BHT DSA-30 water system | <12 µS/cm |
| Hydrochloric acid | HCl | Saarchem | 99% |
| Magnesium sulphate anhydrous | $MgSO_4$ | Saarchem | UNI-LAB |
| Magnesium metal turnings | Mg | Saarchem-Holpro analytic | 99.5% |
| Sodium Nitrite | $NaNO_2$ | Saarchem | 99% UNIV-AR |
| Sodium chloride | NaCl | Merck | 99.5% UNIV-AR |
| Sodium hydroxide | NaOH | Merck | 98% UNI-LAB |
| Sodium carbonate | $Na_2CO_3 \cdot 10\ H_2O$ | Associated Chemical Enterprises | 99% |
| Sodium metal | Na(s) | Holpro | LAB |
| Sulphuric acid | $H_2SO_4$ | Merck<br>Saarchem | 99%<br>98.8% |

### 3.1.2 Reagents for analysis

The reagents used as standards for gas chromatography (GC) and gas chromatography-mass spectrometry (GC/MS) are listed in Table 3.3. All standard materials were used as received.

**Table 3.3: Reagents for analysis**

| Chemical | Formula | Supplier | Grade/Purity |
|---|---|---|---|
| Benzophenone | $C_{13}H_{10}O$ | Aldrich | 99% |
| 4-butoxyphenol | $C_{10}H_{14}O_2$ | Aldrich | 98% |
| 1,4-Benzoquinone | $C_6H_4O_2$ | Aldrich | 98% |
| 1,4-dimethoxybenzene | $C_8H_{10}O_2$ | Aldrich | 99% |
| Ethanol | $C_2H_5OH$ | Merck | 99.5% (GC) |
| 4-Ethoxyphenol | $HOC_6H_4OC_2H_5$ | Aldrich | 99% |
| Hydroquinone | $C_6H_6O_2$ | Aldrich | |
| Methanol | $CH_4O$ | | |
| 4-Methoxyphenol | $C_6H_8O_2$ | Aldrich | 99% |
| 2-Methoxyphenol | $C_6H_8O_2$ | Aldrich | 98% |
| Phenol | $C_6H_5OH$ | Saarchem | UNIV-AR, min 99.5% |

## 3.2 Synthesis of starting materials

### 3.2.1 Preparation of 4-nitrosophenol

4-Nitrosophenol was prepared by using a modification of a previously reported method.[81] Phenol (10.0g; 0.1mol) was dissolved in 200mL of a warm sodium hydroxide solution (4.25g; 0.1mol in 200mL of deionized water) contained in a 500 $cm^3$ round-bottomed flask fitted with a magnetic stirrer. The reaction mixture was cooled to $0^0C$ in a bath of ice. Powdered sodium nitrite (8.0g; 0.1mol) was then added with constant stirring. Once the sodium nitrite was completely dissolved, 5.6M sulphuric acid (22.0g) was added dropwise by means of a separating funnel, supported above the flask, at such a rate that the addition was completed in 150 minutes. Crushed ice was added regularly to the ice bath to maintain the

temperature at $0^0$C. After all the sulphuric acid was added, the reaction mixture was stirred for an additional 1 hour while the temperature was maintained at $0^0$C. The solid 4-nitrosophenol was removed by filtration under vacuum and washed thoroughly with water. The pale yellow product was then dried upon filter paper in the air; the colour changed to dark brown. After recrystallization from petroleum ether, the melting point range was found to be $138^0$-$140^0$C. The product obtained was analyzed by GC and found to be 99% pure based on the GC peak areas. The identity of 4-nitrosophenol was confirmed by GC-MS and IR analysis.

The mass spectrum of 4-nitrosophenol (Figure 3.1) shows the major characteristic fragmentations (m/z=52; m/z=65; m/z=95; $M^+$=123). The infra-red spectrum (Figure 3.2) shows characteristic absorption bands at Vmax ($cm^{-1}$) 3180, 1630, 1560, 1460, 1377, 1160, 1040, 865 and 720.

**Figure 3.1: Mass spectrum of 4-nitrosophenol**

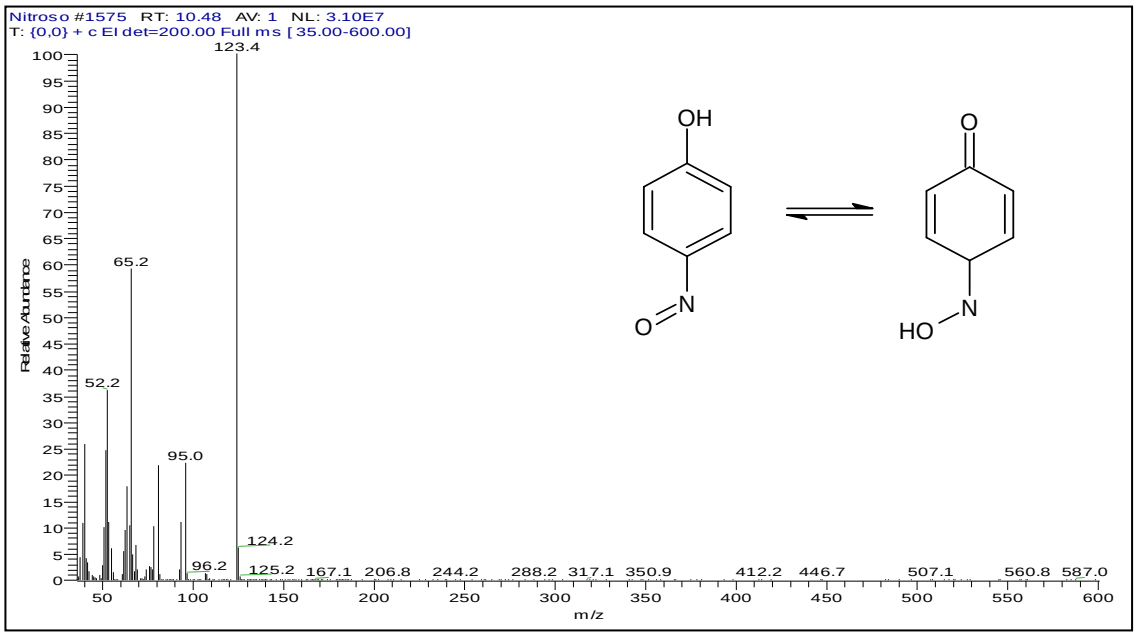
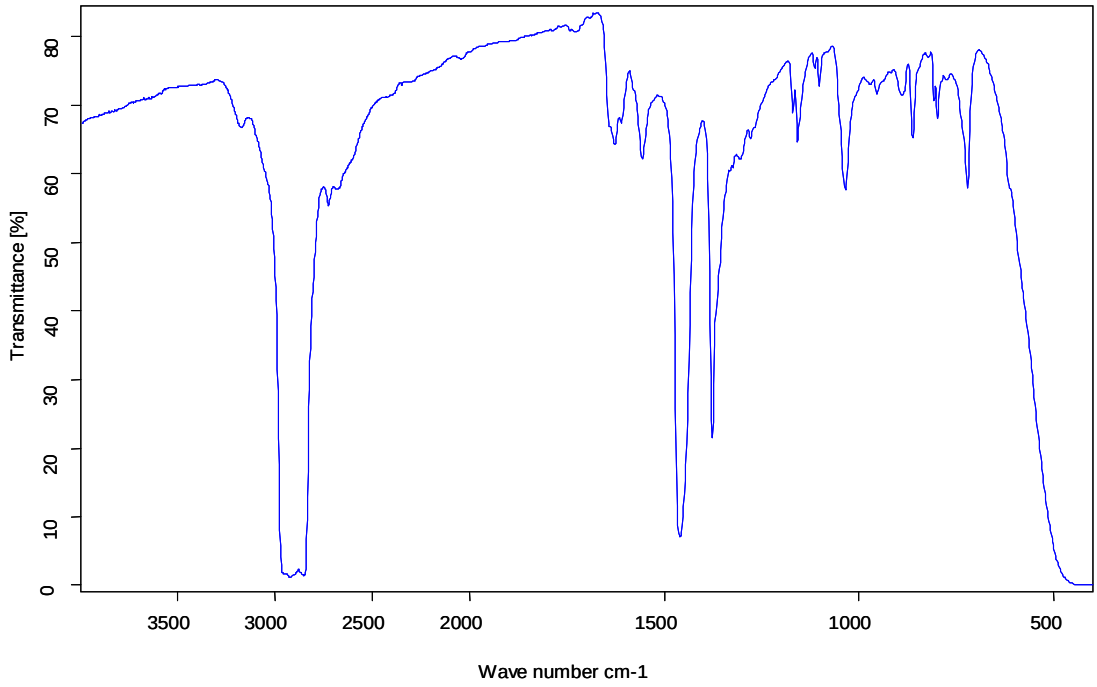


**Figure 3.2: IR spectrum of 4-nitrosophenol**




### 3.2.2 Preparation of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one

4-(Diphenylmethylene)cyclohexa-2,5-dien-1-one was synthesized by means of a Grignard method.[12] Magnesium metal turnings (1.6g; 0.0658 mol) were added into a dry, two-necked round bottom flask (250mL capacity), fitted with a reflux condenser. Sufficient THF (terahydrofuran) was added to cover all the magnesium metal turnings. A dropping funnel containing bromobenzene (10.0g; 0.0636 mol) was connected to the other neck of the flask and the bromobenzene added dropwise with constant stirring. After complete addition of the bromobenzene, the resultant mixture was allowed to cool down to room temperature. The reaction mixture was then refluxed for 2 hours. Methyl 4-hydroxybenzoate (3.0g; 0.0197 mol) dissolved in 10mL THF (terahydrofuran), was added dropwise. After all the methyl 4-hydroxybenzoate was added, the reaction mixture was refluxed for a further 2 hours and cooled to room temperature. An aqueous solution of ammonium chloride (5g, $NH_4Cl$ + 100mL water) was prepared in a 250$cm^3$ beaker and the reaction mixture poured into it. The mixture was then transferred to a separating funnel and 100mL ethyl acetate was added. After shaking the mixture, it

was allowed to separate into two layers, and the organic layer collected. The aqueous layer was washed two times with ethyl acetate (50mL) and combined with the separated organic layer. The ethyl acetate was then removed by rotary evaporation and the resultant viscous liquid cooled in an ice bath until the product crystallized as yellow-orange coloured crystals. The solid was collected by vacuum filtration and recrystallised from petroleum ether. After recrystallization, GC-analysis showed 97% purity (based on GC peak area). The identity of the 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one was confirmed by GC-MS and IR analysis.

The mass spectrum of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one (Figure 3.3) shows the major characteristic fragmentations (m/z=51; m/z=77; m/z=152; m/z=165; m/z=197; m/z=243; $M^+$=274). The infra-red spectrum (Figure 3.4) shows characteristic absorption bands at Vmax ($cm^{-1}$) 1617, 1515, 1485, 1440, 1370, 1280, 1240, 1200, 1170, 1150, 980, 900, 830, 760, 700, 635 and 530.

**Figure 3.3: Mass spectrum of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one**

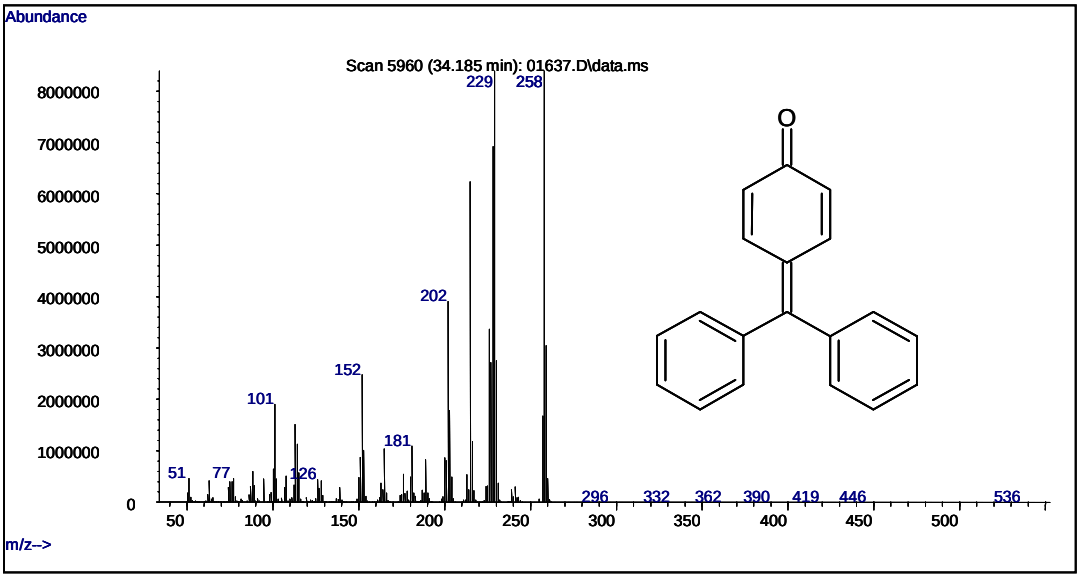
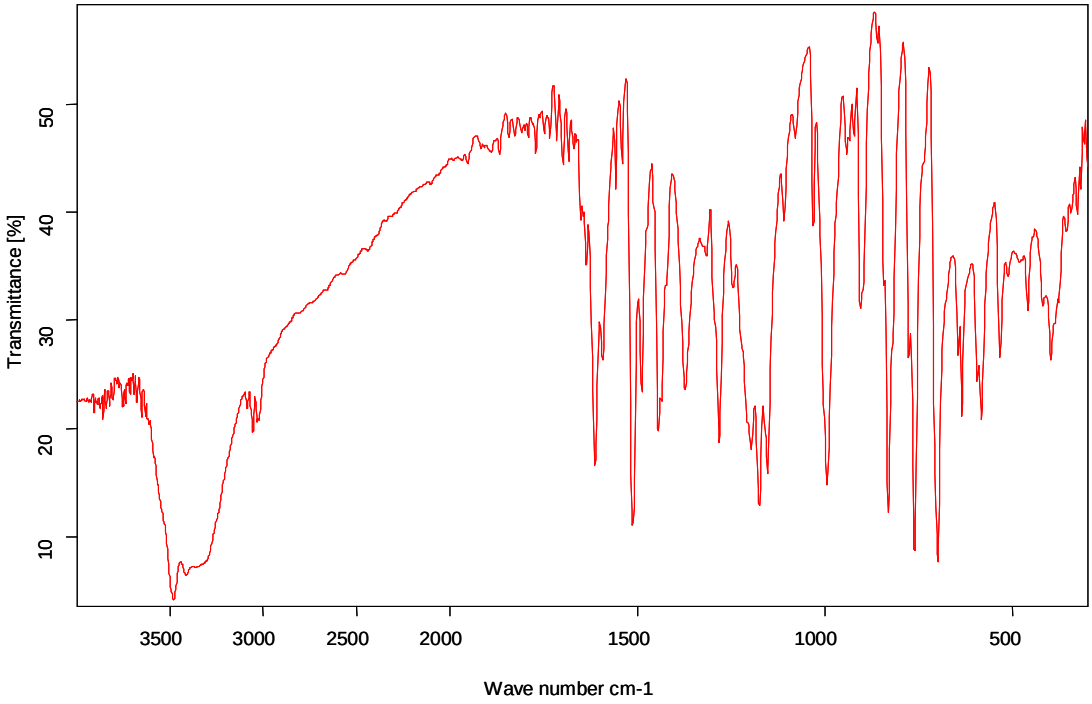


**Figure 3.4: IR spectrum of 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one**




## 3.3 Experimental procedures

### 3.3.1 General procedure for the preparation of 4-alkoxyphenols and reaction set-up

Into a 50mL round bottom flask, 20mL of the appropriate alcohol and required amount of acid were added, after which the required substrates were added to the mixture. The reaction vessel was fitted with a condenser and immersed in a preheated oil bath (Figure 3.5). The resultant mixture was stirred at the required temperature for a predetermined specific time. Aliquots of the reaction mixture were removed from the reaction vessel at regular intervals and analyzed by GC and GC-MS.

**Figure 3.5: Reaction set-up**

### 3.3.2 4-Methoxyphenol isolation

Into a 50mL round bottom flask, 20mL of the methanol and 0.051g of sulphuric acid were added, after which hydroquinone:benzoquinone 1:1 mol (0.9:0.9 mmol) were added to this flask. The reaction vessel fitted with condenser was then immersed in a preheated oil bath. The resultant mixture was stirred at the reflux temperature of methanol ($64.7^0$ C) for 30 minutes. The aliquot of the reaction mixture was removed from the reaction vessel and analyzed in a GC-MS (Figure 3.6). The product 4-methoxyphenol obtained in this reaction was separated by column chromatography. The column used here was 70cm long and was packed to 50cm with silica gel. The solvent system used was 95:5 petroleum ether:ethyl acetate.

The fractions were collected and checked on a TLC plate under the UV lamp. The required fractions were concentrated on a Buchi rotavapour. The product was confirmed by $^{1}H$ NMR (Figure 3.7) and $^{13}C$ NMR (Figure 3.8).

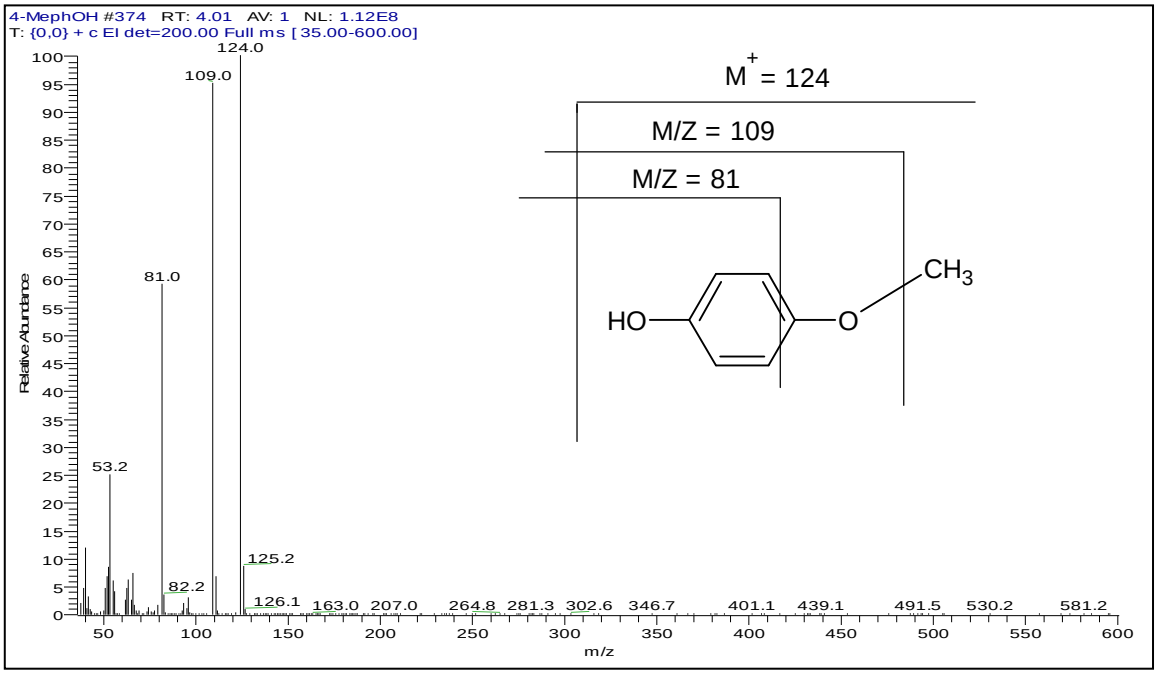
$^{1}H$ NMR (300 MHz, $CDCl_3$) spectral data of 4-methoxyhenol:

The peaks were obtained on give ppm value and the frequencies; δ2.81 (3H, s, Me), 3.7 (1H, br s, OH) and 5.74 (4H, s, Ar H), 1736.52Hz.

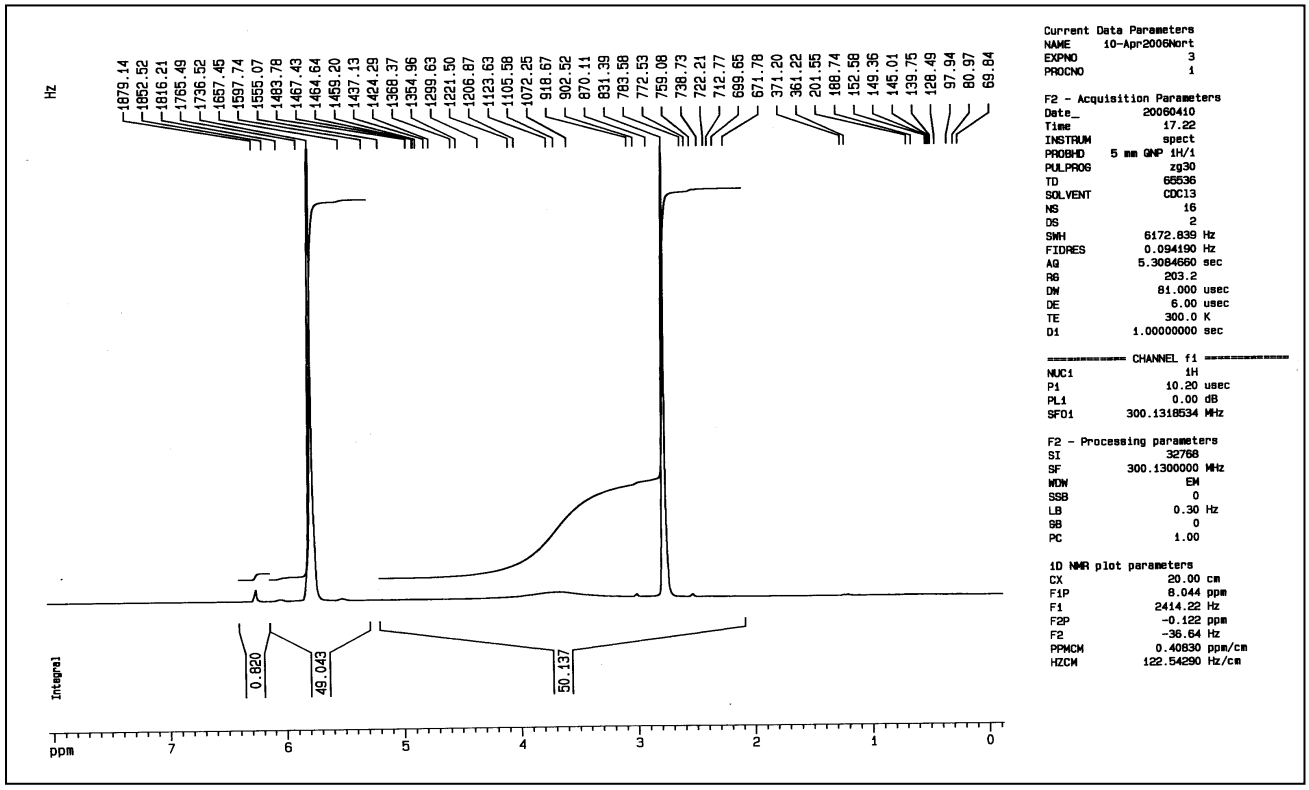
$^{13}C$ NMR spectral data of 4-methoxyhenol:

$^{13}C$ NMR (75 MHz, $CDCl_3$/ppm): δ55.24, 75.99, 76.41, 76.84, 113.53, 114.30, 115.47, 148.88, 153.03.

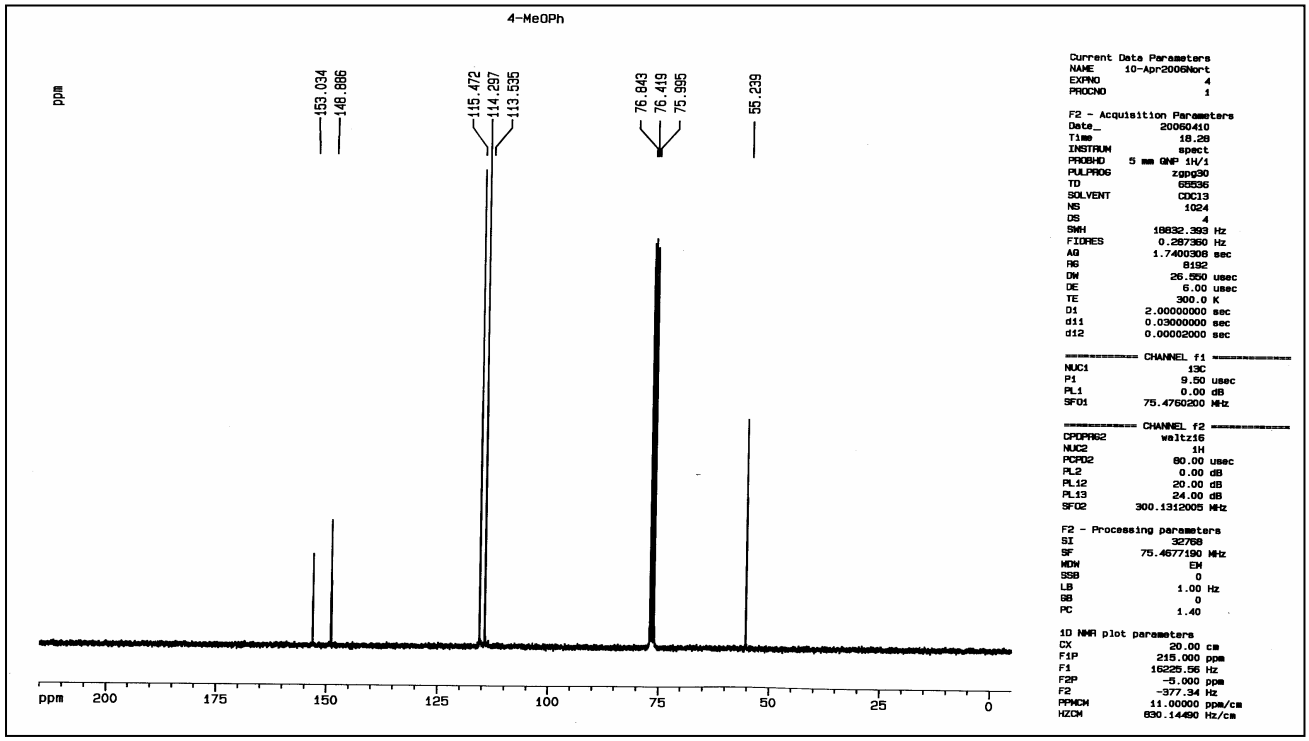
**Figure 3.6: Mass spectrum of 4-methoxyphenol**



## Figure 3.7: $^{1}$H NMR of 4-methoxyphenol




## Figure 3.8: $^{13}$C NMR of 4-methoxyphenol



## 3.4 Product analysis

### 3.4.1 Gas chromatography

All reaction samples were analyzed using a Thermo-Finnigan Focus Gas Chromatograph, equipped with a flame ionization detector, and a JW Scientific, DB-1701 column (film thickness 0.25µm; internal diameter 0.25mm; length 30m). Delta Chromatography software was used for recording and integrating of the chromatograms. Nitrogen was used as carrier gas and the carrier gas flow rate was kept constant at 1mL/min. for all the analyses. The injector and detector temperatures were $280^0$C and $300^0$C, respectively, for the analysis of all the reaction samples. The column temperature program used for hydroquinone-benzoquinone reactions is summarized in Table 3.4 and the column temperature program used for 4-nitrosophenol and fuchsone reactions is given in Table 3.5.

**Table-3.4: Temperature program used for hydroquinone-benzoquinone reaction analyses**

| Column | DB-1701 |
|---|---|
| Initial column temperature ($^0$C) | 70 |
| Initial hold time(minutes) | 5 |
| Heating rate ($^0$C min.$^{-1}$) | 10 |
| Final column temperature ($^0$C) | 260 |
| Final hold time (minutes) | 5 |

**Table-3.5: Temperature program used for 4-nitrosophenol and 4-(diphenylmethylene)cyclohexa-2,5-dien-1-one reaction analyses**

| Column | DB-1701 |
|---|---|
| Initial column temperature ($^0$C) | 70 |
| Initial hold time(minutes) | 2 |
| Heating rate 1 ($^0$C min.$^{-1}$) | 10 |
| Final column temperature 1 ($^0$C) | 135 |
| Final hold time 1 (minutes) | 3 |
| Heating rate 2 ($^0$C min.$^{-1}$) | 3 |
| Final column temperature 2 ($^0$C) | 145 |
| Final hold time 2 (minutes) | 3 |
| Heating rate 3 ($^0$C min.$^{-1}$) | 15 |
| Final column temperature 3 ($^0$C) | 270 |
| Final hold time 3 (minutes) | 3 |

### 3.4.2 Gas Chromatography-Mass Spectroscopy

GC-MS analyses were performed on a Thermo-Finnigan Trace GC coupled to a Quadropole Trace MS$^+$ detector. A Restek-RTX 5 MS (15m x 0.25mm internal diameter) column was used for analysis. Data was acquired from the detector by means of a Bell personal computer equipped with Excaliber version 1.3 software. The temperature program used for analyses is shown in Table-3.6.

**Table-3.6: Temperature programme used for GCMS analyses**

| Column | RTX 5 MS |
|---|---|
| Initial column temperature ($^0$C) | 70 |
| Initial hold time(minutes) | 5 |
| Heating rate ($^0$C min.$^{-1}$) | 10 |
| Final column temperature ($^0$C) | 270 |
| Final hold time (minutes) | 5 |

### 3.4.3 Nuclear Magnetic Resonance (NMR) Spectroscopy

$^1$H NMR spectra were recorded on a Brucker AX (300 MHz) spectrometer using X-Win NMR software for data analysis. All samples were analyzed using $CDCl_3$ as solvent.

### 3.4.4 Infra red (IR) Spectroscopy

Infra red spectra were recorded on a Brucker Tensor 27 FTIR linked to a Bell computer, equipped with Opus software version 4.2. All samples were analyzed by using $CCl_4$ as solvent.

## 3.5 Calculating response factor and corrected peak areas

The calculation of substrates and product mol percentages were done by using the reported method.[82] The substrates and product peak areas ($PA_i$) were calculated by the GC flame ionization detector (FID) signal integrator. A peak area represents the integral of the intensity of the FID signal of a peak over time. Thus the peak area is a measure of the amount of carbon eluted with a peak and also of the intensity of carbon atom ionization within the particular component. The intensity of the FID signal is dependent on the nature of atoms bonded to a carbon atom, as each carbon atom will give a different intensity depending on its environment (e.g. carbon-carbon and carbon-hydrogen gives equal signal intensity, while carbon-oxygen gives different, namely lower, signal intensity).

Thus the intensity of the FID signal needs to be corrected for the carbon atoms bound to oxygen atoms in the respective component. The average response factor ($f_i$) for a particular species considers the different response in the FID of a carbon atom in the molecule that is bound to oxygen atoms. For example, the response of a carbon atom when only bonded to carbon or hydrogen equals 1, but a carbon atom with a single bond to an oxygen atom has been determined experimentally to only have a response of 0.55 and carbon atoms double bonded to oxygen give a response of 0 (Callanan van Steen, 1999). Response factors, $f_{i,}$ for molecule were calculated on this basis. Peak areas of oxygen compounds must be multiplied by these factors to obtain a “corrected peak area”, which is proportional to the amount of carbon eluted with that particular peak.

Response factors were calculated by using the following formula:

$$Rf = \frac{total\ number\ of\ carbon\ atoms\ of\ particular\ compound}{response\ of\ carbon\ atmos\ of\ particlar\ compound}$$

where ‘Rf’ is the response factor of a particular compound.
As an example of response factor calculation, that of hydroquinone is as follows:

$$Rf = \frac{6}{4 \cdot 1 + 2 \cdot 0.55} = \frac{6}{5.1} = 1.176$$

This response factor is used to calculate corrected peak area ($CPA_i$) by multiplying with peak area ($PA_i$) as obtained from the GC trace of the particular compound. The formula is given below:

$$CPA = PA\ x\ Rf$$

For the molar basis conversion, corrected peak areas ($CPA_i$) were converted into mol proportional values ($PAM_i$). $PAM_i$ is effectively peak area over response of carbon atoms in the molecule. Molar basis conversion was calculated by the following formula:

$$PAM = \frac{CPA}{number\ of\ carbon\ atoms\ in\ particular\ compound}$$

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