

THE ROLE OF SILICA GEL
IN THE SOLID-PHASE-CATALYZED
FRIEDEL-CRAFTS *tert*-BUTYLATION OF HYDROQUINONE

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Abstract

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The use of silica gel as an acidic catalyst for the Friedel-Crafts alkylation of hydroquinone with *tert*-butyl bromide affords 2,5-di-*tert*-butylhydroquinone in high yield and purity if sodium carbonate is also present. Drying the sodium carbonate in a furnace (275 °C) effectively stops this Friedel-Crafts alkylation. Hence, a trace amount of water serves a necessary role as cocatalyst. Isobutene and its olefinic dimers are formed in small amounts from *tert*-butyl bromide during the reaction; however, isobutene is not the source of the electrophilic intermediate in the Friedel-Crafts *tert*-butylation because the extent of alkylation in a closed reaction vessel is the same as that obtained when the stirred and heated reaction was conducted in an open system whose thermostated reflux condenser was kept at temperatures above the boiling point of isobutene.

A proton NMR technique of multicomponent, trace-organic analysis was developed to distinguish the numerous, minor byproducts and also to quantify the product distribution. It is expected that application of this analytical method in kinetic and other experiments will contribute to a better

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understanding of the role of silica gel in the mechanism of the reaction. Although the reaction mixture has a somewhat complicated NMR spectrum with many peaks in the aromatic, olefinic, hydroxyl, and alkyl regions, the spectra of all components were discernible, and most of them have now been distinguished by comparison with the spectra of 16 reference compounds.

Since the Doctor of Arts is fundamentally a college teaching degree, an extra chapter entitled "Educational Implications" provides a detailed review of the microscale literature. The greater environmental awareness of current students, the expense of operation, and the force of law brought about by inclusion under OSHA's regulations have caused concerned academic chemists to seek alternatives to standard laboratory practices and have raised doubts as to the viability of undergraduate laboratories. Microscale experimentation may have diverted the conversation from more radical solutions, but the ultimate fate of lower-division laboratories in chemistry is not yet certain.

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CHAPTER 1

Introduction

The present research topic is based on the relatively recent report that silica gel has been used as an acidic catalyst in a heterogeneous reaction to achieve a Friedel-Crafts *tert*-butylation of hydroquinone.¹ A Friedel-Crafts reaction is a type of electrophilic aromatic substitution discovered jointly by Charles Friedel^{2,3} and James Mason Crafts^{4,5} in 1877.

Friedel and Crafts coauthored^{5,6} nearly one hundred scientific papers during their 17-year collaboration, about half of which contain a body of experimental evidence that demonstrates the role of aluminum chloride and other Lewis acids as the catalyst of numerous reactions for organic synthesis.^{7,8} This effort included reactions of organic halides and olefins with aromatic and aliphatic compounds (Friedel-Crafts alkylation); reactions of the halides and anhydrides of carboxylic acids with aromatic compounds (Friedel-Crafts acylation); reactions of oxygen, sulfur, sulfur dioxide, carbon dioxide, and phosgene with aromatic compounds; the desulfurization, catalytic cracking, and isomerization of aliphatic and aromatic compounds; and the polymerization of olefins. These results were achieved in the second collaboration of Friedel and Crafts mainly at

l'École des Mines of the University of Paris (1874-1891), their first being joint studies of organosilicon compounds in Wurtz's laboratory at l'École de Médecine (1863-1865). Their pioneering efforts became the foundation of what is now referred to as Friedel-Crafts and related reactions. The numerous reviews in the older Russian literature⁹ were, perhaps, inspired by the now abandoned claim that a Russian chemist deserved priority for discovering the "Gustavson-Friedel-Crafts reaction."

Friedel-Crafts technology has grown in scope¹⁰ and is today a vital process in industrial organic chemistry.¹¹⁻¹⁵ The early literature of this reaction has been extensively reviewed,¹⁶⁻²⁶ especially in the treatise edited by George Olah which, when terminated in 1965, was embodied in four volumes of six parts containing over 5000 pages.²⁷ Olah published a briefer monograph⁷ in which five chapters of his comprehensive treatise were updated and reprinted with new chapters covering progress through 1972. Subsequent developments in the field of Friedel-Crafts alkylation chemistry are contained in the important book (790 pages) of Roberts and Khalaf,⁸ the former author being prominent in the primary literature.²⁸ Friedel-Crafts and related reactions are also included in the "Electrophilic Aromatic Substitution" chapter of the annual survey entitled *Organic Reaction Mechanisms*, for which the most recently published volume is cited.²⁹

The field of Friedel-Crafts chemistry is currently so diverse that a concise definition is arduous to formulate, but the broad interpretation of Olah³⁰ is still commonly accepted; namely, that a reaction can be classified as a Friedel-Crafts if any addition, substitution, elimination, polymerization, cracking, or isomerization occurs due to the catalysis of a Lewis acid (e.g., AlBr₃, AlCl₃, FeCl₃, SbCl₅, BF₃, SnCl₄, or ZnCl₂; with or without cocatalysts) or a protic acid (e.g., HF, H₂SO₄, H₃PO₄, or HSO₃F).

Organic compounds that have been employed as potential electrophiles in Friedel-Crafts aromatic electrophilic substitution reactions include alkyl halides, alcohols and mercaptans, epoxides, ethers and sulfides, alkyl esters, sulfates and sulfonates, and olefins for alkylation^{8,17,31} and carboxylic acids, acid anhydrides, aryl esters, amides, ketenes, and especially acyl halides for acylation.^{21,22,32} Other closely related acid-catalyzed aromatic electrophilic substitutions^{33,34} include haloalkylation with aldehydes and hydrogen halides,²³ formylation with carbon monoxide (the Gattermann-Koch reaction)²⁴ or inorganic cyanides (the Gattermann reaction),²⁵ acylation with nitriles (the Hoesch or Houben-Hoesch reaction),²⁶ and many others discussed by March³⁵ such as the Scholl arylation reaction.

Necessarily, the present discussion is limited to the Friedel-Crafts tert-butylation of aromatic compounds with alkyl halides³⁶ because this reaction was the one utilized

in the present investigation. The literature cited in the preceding paragraphs document a few points about this particular type of Friedel-Crafts alkylation that should be reiterated in connection with the results that are reported in Chapter 3:

1. A free carbocation or an ion pair³⁷ derived from the alkylating agent is often, but not always,^{33,34} proposed as the electrophile in the reaction mechanism of Friedel-Crafts alkylation^{7,8,27,38} and is almost certainly the electrophilic intermediate during tert-butylation.^{39,40} Thus, the reactivity order for all types of alkylating agents^{41,42} is allylic/benzylic > tertiary > secondary > primary > methyl; however, this also means that rearrangement of the carbocation and/or polymerization of the alkylating agent is possible and is frequently observed. Tert-butylation, unlike tert-pentylation,^{20,43} is not complicated by rearrangement within the alkyl group.⁴²
2. The relative reactivity of alkyl halides and the much less reactive aryl halides as likely electrophiles for the alkylation or arylation of aromatic compounds is $R-F > R-Cl > R-Br > R-I$, which is generally the reverse of their reactivity in other types of reactions and is also opposite the order of reactivity for the analogous acyl halides during Friedel-Crafts acylation.^{40,44} Frequently, a linear free energy relationship is used to describe the reactivity of the attacking electrophile in terms of the thermodynamic quantity "acidity" (carbocations are Lewis acids) and the kinetic quantity of "electrophilicity," which bear the same kind of relationship as between "basicity" and "nucleophilicity" when used for nucleophile in nucleophilic substitutions.⁴⁵

3. There is a general tendency for successive alkylations to produce polyalkyl derivatives, although this often can be controlled by the choice of reaction conditions. The increased reactivity of the initial product towards further alkylation is only partly caused by the small activation effect of its newly acquired *ortho-para* directing alkyl group and is mostly due to the greater solubility of the alkylated product in the catalyst layer, in which the reaction is thought to occur.⁴⁶ The extent of polyalkylation is also limited by the amount of steric interaction that can be tolerated in the final product.⁴⁷⁻⁴⁹
4. Steric hindrance is significant in the case of *tert*-butylation and dominates the *ortho-para* ratio by limiting the amount of *ortho-dialkyl* product formed.⁵⁰ Alkyl substituents normally activate the *para* position in the Baker-Nathan order^{51,52} of methyl > ethyl > isopropyl > *tert*-butyl in most electrophilic substitutions instead of the reverse order expected from an inductive effect alone.^{38,53} Such kinetic control is promoted by reagents having high electrophilicity and in reaction mediums of low nucleophilicity.⁵⁴
5. Alkylations under Friedel-Crafts conditions are frequently reversible, and dealkylation, intramolecular reorientation, and/or intermolecular disproportionation (causing transalkylation) of the initial product may occur as a minor process or, under suitable conditions, as the predominate reaction.⁵⁵ Thus, the orientation of substitution in the product is often thermodynamically and not kinetically controlled. The *tert*-butyl group is particularly easy to displace from an aromatic nucleus under Friedel-Crafts conditions.^{56,57} Reversible reactions,^{38,55} except for the special case of the Jacobsen

rearrangement with sulfuric acid,⁵⁸ reach a thermodynamic equilibrium where enthalpy differences (i.e., steric factors) disfavor substituents having an *ortho* relationship and entropy differences (i.e., statistical factors) favor *meta* over *para* substituents.

6. When Friedel-Crafts alkylation is attempted on phenolic compounds,^{9,59,60} O-alkylation to form an alkyl aryl ether can compete with C-alkylation of the aromatic ring;^{50,61,62} however, rearrangement of the phenolic ether is also possible under these conditions,⁶³ which can often be varied to favor migration of the alkyl group from the oxygen to either the *ortho* or *para* position on the benzene ring similar to the Fries rearrangement of phenolic esters.⁶⁴ Phenols,⁵⁹ including hydroquinone, and phenolic ethers⁶⁵ normally possess an aromatic ring that is activated for aromatic electrophilic substitution, but the potential basicity of the lone electron pairs of these groups⁶⁶ allows coordination with Lewis acids and protonation by Brønsted-Lowry acids under Friedel-Crafts conditions to cause deactivation of the aromatic ring. Even under such conditions, a phenolic group retains its *ortho-para* directing ability,⁶⁷ but exceptions are known where steric factors outweigh electronic ones⁶⁸ and, conversely, where steric interaction is ignored to such an extent that the *ortho* product is greatly favored over the *para*.^{58,69,70}
7. While the conditions of many Friedel-Crafts alkylation procedures are reported to be "anhydrous," a trace amount of water often serves a beneficial and even necessary role as a cocatalyst.⁷¹

The innate difficulties for Friedel-Crafts alkylation of aromatic compounds are many and complex, but a common

cause of poor yields and lack of specificity was summarized with rhetorical simplicity and current suitability in W. S. Johnson's now dated review as "reaction conditions which are too drastic and reagents of inadequate purity."²² The more reactive catalysts cause undesirable side-reactions,⁷² and the catalyst chosen is usually one just active enough to effect the alkylation at a reasonable rate. Hojo and coworkers¹ restated the problems associated with the use of strong Lewis acid catalysts in Friedel-Crafts alkylations and proposed the use of silica gel as a mild and selective acidic catalyst. Hojo et al reported that heterogeneous reaction mixtures involving silica gel caused successful Friedel-Crafts alkylations of selected phenolic compounds and heterocyclic aromatics when using *tert*-butyl bromide and other alkylating agents. This was but one of a series of papers⁷³ on applications of solid catalysis to organic synthesis reported by Masaru Hojo at Kobe University (Department of Industrial Chemistry, Faculty of Engineering).

One particular silica gel catalyzed Friedel-Crafts alkylation mentioned by Hojo¹ was the *tert*-butylation of hydroquinone shown in Figure 1, which was employed as the basis for the present research topic. In this procedure, 0.22 g (2 mmol) of hydroquinone in 7 mL of CCl₄ was heated with 1.00 g of silica gel, 0.95 g (9 mmol) of powdered sodium carbonate, and 0.82 g (6 mmol) of *tert*-butyl bromide

at 70 °C for 24 h to afford a 92% isolated yield (100% GC conversion) of the product, 2,5-di-*tert*-butylhydroquinone. The heterogeneous catalyst simplified the workup, which consisted only of filtering and washing the solids with ether and isolating the product through evaporation of the filtrate.

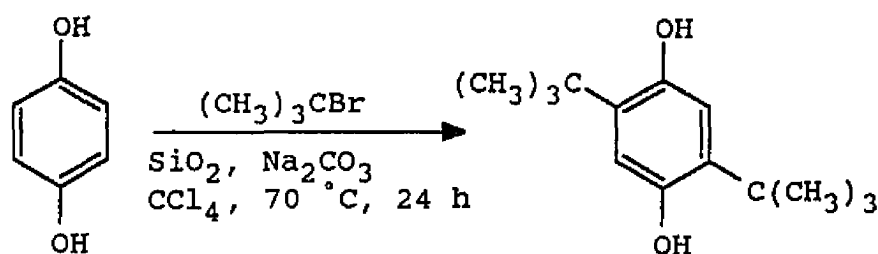


Figure 1. The Friedel-Crafts *tert*-Butylation of Hydroquinone by the Method of Hojo.

This reaction is a significant use of heterogeneous catalysis,⁷⁴ which is increasingly employed as a synthetic method⁷⁵⁻⁸⁰ to avoid harsh reaction conditions, increase yield, and improve selectivity.^{81,82} These may be due to either a lowering of the activation energy of reactants by their interaction with polyelectrolytic surfaces or simply because local accumulations of molecules within confined spaces on the surface of the catalyst are more likely to collide. Also, these reactions often "break the rules" by producing the kinetically favored products rather than the thermodynamically more favored products from equilibrating

reaction mixtures.¹ Speculation for this increased level of selectivity has included such factors as: lower reaction temperatures, increased concentration of the reactants and solvent near the surface, shape selectivity of the pores, variations in energy levels created by the interaction of the reactants with the surface, and/or privileged modes of activation due to vibrational coupling with the catalyst. Furthermore, the solid catalyst is removed by filtration, thereby causing little contamination of product or solvent. Even when extremely reactive reagents are adsorbed on the surface of silica gel, they pose considerably less danger in handling than is usually associated with the unsupported reagent.

The solid may be the sole catalytic agent or may have the more passive role as a support for other reagents or catalysts.⁷⁷ Examples of both uses are found in two recent Ph.D. dissertations, the first of which is a study of the decomposition of anisoyl and benzoyl peroxides on silica gel's surface,⁸³ while the other describes the use of an acidic clay (montmorillonite K10) to support Lewis acids for Friedel-Crafts alkylation of benzene by benzyl chloride followed by oxidation of the product diphenylmethane into benzophenone using a supported oxidizing agent.⁸⁴

Numerous similar organic reactions have been conducted with inorganic solids⁷⁶ such as silica gel,^{73,85} alumina,⁸⁶ aluminosilicates^{79,87-89} (zeolites and clays), and carbon

allotropes,^{76,90} and with reagents supported by organic matrices⁹¹⁻⁹³ (polymer-supported and ion-exchange resins) including recently developed solid super acids.⁹⁴ Metals, metallic oxides, and organometallic compounds continue to perform a defining role as heterogeneous catalysts^{11,95-99} in industrial processes and laboratory synthesis; however, only silica gel will be discussed here due to the extensive coverage of heterogeneous catalysis in the literature, but the general principles concerning silica gel often apply to the various other solid catalysts.

Although possessing superior theory and experimental techniques,¹⁰⁰⁻¹⁰⁴ the modern synthetic chemist wishing to describe heterogeneous reactions is in a situation parallel to the chemists of the last century describing homogeneous reaction systems in that they both lack specific knowledge about the nature of the reaction at the atomic level. The modern chemist may use terms such as "acidic active sites" to convey the idea that surface events have happened in much the same way as the archaic term "affinity" was used. Goldstein illustrates this by suggesting that the idea of acidity, when used to describe the catalytic activity of solid surfaces, may only be a plausible explanation for the occurrence of product and should not be taken as genuine understanding about the nature of the surface reaction.¹⁰⁵

Nevertheless, it is thought that hydroxyl groups on the surface of the silica gel, called silanol groups, are

the active sites for acid catalysis. There is an average of five silanol groups per nm^2 on the surface of silica gel as measured by a number of different procedures.¹⁰⁶⁻¹⁰⁸ To describe the acidity of the silanol group, it is necessary to deduce its environment; however, there is not one, but several types of silanols^{85,108-112} described variously as associated (hydrogen-bonded), isolated, vicinal, geminal, or embedded. Each of these has its own energy parameters and, consequently, different catalytic properties. This does not include the hydroxyls of water that can be and usually are adsorbed on each silanol type whether on the surface, in pores, or embedded in the bulk. The meager acidity of silica gel, whose pK_a values range from about 5 to 9 for the various silanol groups,^{108-110,113} caused Olah to discount its use as a Friedel-Crafts catalyst in favor of the much more acidic aluminosilicates.⁷⁵ This fact notwithstanding, silica gel is the sole catalyst in many procedures.^{73,85,113} Currently, hydrogen-bonded geminal silanol groups are considered more acidic (pK_a 5-7) than their isolated counterparts (pK_a 9.5) and are generally regarded as the active sites.⁸¹

While a catalytic amount of water is often needed for Friedel-Crafts reactions,⁷¹ too much water can poison the catalyst. Silica gel must be heated above 105 °C in order to remove the physisorbed surface water at 760 mmHg and at temperatures greater than 200 °C to start the removal of

water in pores and in subsurface sites, although this can be achieved at lower temperatures under vacuum. Even under reduced pressure, temperatures must exceed 200 °C before the hydrogen-bonded vicinal silanols start to condense into water, thus reducing the number of silanol groups available as active sites. This process continues¹¹⁴⁻¹¹⁷ until only nonhydrogen-bonded silanols (either isolated or geminal) remain when temperatures reach 400 to 600 °C. Activating temperatures from 650 to 800 °C initiate the progressive loss of the isolated silanol groups,¹¹⁸ which also causes a decrease in the catalytic activity towards polar molecules due to the relative increase in the amount of hydrophobic surface. A fully hydrophobic surface occurs above 850 °C and sintering begins at about 900 °C.¹¹¹

Although the mechanism for the catalytic ability of silica gel is poorly understood, the various kinds of interactions that molecules and ions have with its surface and in its pores is clearly important. The pores in silica gel can be made in various sizes by carefully controlling the conditions of its manufacture.^{102,107,113} Commercial silica gels¹¹³ are generally either of the narrow-pore type (average pore diameter about 2.5 nm, specific area about 700 m²/g, and mean pore volume about 0.4 cm³/g) or of the wide-pore type (average pore diameter about 14 nm, specific area about 300 m²/g, and mean pore volume about 1.1 cm³/g); however, other grades of silica gels have pore diameters

that range from one to several hundred nm.¹⁰⁷ Silanol groups within the pores are especially adsorbent, which is due to the surface's negative curvature inside the pore that moves the silanol groups closer together.¹⁰⁹ Thus, silica gels can be designed for individual target molecules and solvents by varying the size of their pores to match the sizes of these molecules or their transition states during reaction, which increases the selectivity obtained for specific reactions.

The original goal for the initial research proposal was to discover the role of silica gel in Hojo's procedure for the Friedel-Crafts *tert*-butylation of hydroquinone with *tert*-butyl bromide.¹ Although the current study did not elucidate the role of silica gel, it did develop a successful proton NMR method of multicomponent trace-organic analysis whose application may contribute to the solution. Careful examination of the products and byproducts of a reaction often suggests a mechanism for the major pathway because the validity of any mechanistic proposal is tested by its ability to correctly predict all of the components of the product distribution, both those derived from the substrate and those from the various reagents employed.¹¹⁹ Although there are many examples where this approach has been successful in elucidating reaction mechanisms,^{120,121} there is no a priori certainty that the mechanism initially suggested is the correct one,

nor that the major and minor products share the same mechanism, nor that an unambiguous or even sensible conclusion can be obtained.¹²² This type of approach, then, is suggestive rather than absolute, but its potential cannot be known until it is tried.

CHAPTER 2

Materials and Methods

Materials

The ^1H NMR spectra of the organic compounds described in this section are summarized in Table III of Chapter 3. They were all recorded from carbon tetrachloride solutions containing 1 vol % tetramethylsilane (TMS) and 30 vol % of acetone- d_6 , this last component of the mixed-solvent system serving the dual functions of providing deuterium for the NMR lock signal and enhancing the solubility of the diverse compounds whose solutions were prepared. TMS provided the internal reference for chemical shift and was acquired in NMR grade from Norell, Inc. (catalog no. DC1320). Isotec, Inc. supplied the acetone- d_6 (99.9 atom % D, catalog no. 82-00732) sealed in glass ampules having one-gram portions. Exchangeable protons were identified¹²³ by the addition of a few drops of either deuterium oxide obtained from Norell, Inc. (99.96% D, catalog no. DC1100) or trifluoroacetic acid from the Eastman Kodak Company (99%, catalog no. 188-3763) as a fuming, colorless liquid.

The grade and handling of the silica gel and sodium carbonate employed in the *tert*-butylation reaction were identical with specification given by Hojo *et al* in the literature.¹ The silica gel (used as the acidic catalyst)

was Wakogel C-300 from Wako Pure Chemical Industries, LTD. (catalog no. 234-00085, lot no. WEM7348). Wakogel C-300 can be bought from Wako Chemicals USA, Inc., 1600 Bellwood Road, Richmond, VA 23237 as a white, free-flowing, 200-300 mesh powder. It was dried at 170 ± 2 °C for at least five hours under a reduced pressure of 4 ± 1 mmHg in a Precision Scientific, Inc. (GCA Corporation) model 19 vacuum oven, then was cooled to room temperature for one-half hour in a desiccator over a mixture of anhydrous calcium chloride and indicating Drierite immediately preceding use. The inlet vent of the vacuum oven was equipped with a gas-drying jar having a 6 x 20 cm column containing approximately 550 g of indicating Drierite. Specifications from the manufacturer for the vacuum oven were ± 1 °C sensitivity and temperature uniformity of ± 3 and ± 5 °C at 100 and 200 °C, respectively, in its stainless steel working chamber having a 0.014 m^3 interior. The activation temperature reported is the mean and range of typical values that were measured by using a Taylor no. 5973 bimetal oven thermometer placed near the silica gel.

Anhydrous sodium carbonate, obtained in ACS reagent grade from Fisher Scientific (catalog no. S-263), was finely powdered by grinding 4-5 min with an agate mortar and pestle and, following Hojo et al.,¹ was used directly in most experiments without drying in an oven. In order to test the effect of moisture in the sodium carbonate on the

tert-butylation reaction, some samples were dried¹²⁴⁻¹²⁶ at 275 °C in a partially covered, 20-mL porcelain casserole using a Lindberg Hevi-Duty model 51441 box furnace that was preheated overnight at the drying temperature. The furnace temperature was monitored using a platinel II thermocouple and was recorded to the nearest ± 5 °C from the pyrometer of the Lindberg 59344 time-proportioning, temperature-control console.

Carbon tetrachloride, used as a solvent for both the tert-butylation reaction and the solutions for proton NMR spectra, was obtained in ACS reagent grade from J. T. Baker Chemical Company (catalog no. 1512). It was purified¹²⁷ by refluxing over phosphorous pentoxide for 18 hours, then was distilled at 0.5 mL/min (1.9:1.0 reflux ratio) through a Hempel-type distilling column having an electrically heated jacket¹²⁸ and packed with one-eighth inch glass helices on its honeycomb packing support, which provided an effective fractionating volume of 2.0 x 24 cm. Collecting the middle fraction by discarding the first and last 13% (by volume) afforded a clear and colorless distillate, bp 76.2 ± 0.1 °C at 748 mmHg (cor) [lit.¹²⁹ bp 76.75 °C (760 mmHg), dt/dp = 0.04320 °C/mmHg], which was stored protected from light over 4A molecular sieve. Ultraviolet absorbances recorded at selected wavelengths for both unpurified and purified solvent are compared with ACS Reagent Grade criteria¹³⁰ in Table I.

Table I

UV Absorbances of the Carbon Tetrachloride Solvent at Selected Wavelengths

Wavelength, nm	Absorbance, A (mean of n = 3 spectra)		
	J. T. Baker ACS Grade	Purified Solvent	ACS Reagent ¹³⁰ Grade Criteria
265	0.82 ± 0.04	0.60 ± 0.02	< 1.00
270	0.44 ± 0.02	0.25 ± 0.01	< 0.35
280	0.201 ± 0.002	0.047 ± 0.001	< 0.10
290	0.120 ± 0.001	0.011 ± 0.001	< 0.05
300	0.070 ± 0.001	0.004 ± 0.001	< 0.02
330	0.015 ± 0.001	0.001 ± 0.001	< 0.01
400	0.000 ± 0.001	0.000 ± 0.001	< 0.01

Ultraviolet (UV) spectra were recorded against reagent grade water on a Cary model 17D automatic-recording spectrophotometer using a matched pair of 3.0-mL cells from Fisher Scientific (Fisherbrand no. 14-385-904D) having 10.00 ± 0.01 mm path length, SUPRASIL (far UV quartz) windows, and a tapered PTFE stopper. A baseline for the empty sample cell against the water blank was also obtained and was employed to determine the true absorbance of the sample. All spectra were recorded using automatic slitwidth control and a scanning rate of 0.5 nm/s from 400 nm to the UV cutoff ($A = 1.000$), which was measured as 262.2 ± 0.2 nm for purified carbon tetrachloride and 263.6 ± 0.4 nm for the original ACS grade solvent. A 1.0 absorbance full scale was employed together with 15 nm/inch chart drive, slit control = 2, and pen period = 1 s.

The other solvents were used directly without further purification. Fisher Scientific supplied anhydrous ethyl ether (catalog no. E-138), hexanes (catalog no. H-292), methanol (catalog no. A-412), methylene chloride (catalog no. D-37), and toluene (catalog no. T-289 and T-324), all in ACS reagent grade, and *n*-pentane (catalog no. P-400) in pesticide grade. Absolute ethanol was obtained from the Quantum Chemical Corporation, USI Division, in USP grade (200 proof punctilious) and, unlike the previous solvents, was stored over 3A molecular sieve. Quantum Chemical also supplied 95% ethanol in USP grade.

The 3A and 4A molecular sieve^{131,132} were obtained in the form of 8-12 mesh beads from the J. T. Baker Chemical Company (catalog no. 2710 and 2708) and were employed to dry solvents without further activation. Activated coconut charcoal (8-12 mesh) was obtained from the Sargent-Welch Scientific Company (catalog no. C11368) and was used in both a nitrogen-purging system and in a column attached to the reaction vessel during certain isobutene-entrapment experiments.¹³³ Indicating Drierite¹³⁴ is 10-20 mesh granules of anhydrous calcium sulfate impregnated with cobalt(II) chloride from the W. A. Hammond Drierite Company and was regenerated by heating at 200-225 °C for several hours in a box furnace. Anhydrous calcium chloride was obtained from Fisher Scientific (catalog no. C-614) in the form of 4-20 mesh beads.

2-Bromo-2-methylpropane (*tert*-butyl bromide), obtained from Eastman Kodak Company (catalog no. 112-6937) in Kodak reagent grade as a pale yellow liquid, was distilled twice through a Vigreux column (ca. 130 mm indent section) at 0.9 ± 0.2 mL/min throughput discarding the first 25% and last 10% portions of each charge to afford a clear and colorless distillate, bp 72.6 ± 0.2 °C at 745.9 ± 0.1 mmHg (cor) [lit.¹³⁵ bp 73.25 °C (760 mmHg)]. 2-Chloro-2-methylpropane (*tert*-butyl chloride), obtained from Fisher Scientific (99.4%, catalog no. O-1875) in "certified grade" as a colorless liquid, was distilled twice at 0.6 ± 0.1 mL/min discarding the first and last 25% portions to afford a clear and colorless distillate, bp 50.1 ± 0.2 °C at 745.4 ± 0.1 mmHg (cor) [lit.¹³⁶ bp 50.7 °C (760 mmHg), dt/dp = 0.040 °C/mmHg].

The 2-methyl-2-propanol (*tert*-butyl alcohol), obtained from Fisher Scientific (catalog no. A-401) in "certified grade," was purified through six crystallizations from its melt,¹³⁷⁻¹³⁹ taking care to minimize exposure to moisture in the atmosphere. This was accomplished by placing the bottle in a refrigerator overnight to freeze the sample, then inverting the sealed bottle in the laboratory for one day to drain any melt. After the accumulated liquid was discarded and the screw cap of the bottle resealed with Parafilm, it was placed in a bath of warm water to melt the remaining sample and was returned to the refrigerator for

continuation of the procedure until the *tert*-butyl alcohol remained a solid at room temperature indefinitely.

Aldrich Chemical Company, Inc. supplied the isomeric isobutene dimers (disobutenes) 2,4,4-trimethyl-1-pentene (99%, catalog no. T7,840-9) and 2,4,4-trimethyl-2-pentene (99%, catalog no. 14,382-0), and 2,2,4-trimethylpentane (isooctane) was obtained in ACS reagent grade from J. T. Baker Chemical Company (catalog no. 9478), all of which were employed without further purification. HPLC grade *tert*-butyl methyl ether was acquired from Aldrich Chemical Company, Inc. (99.8%, catalog no. 29,321-0) and was dried with 4A molecular sieve. The di-*tert*-butyl dicarbonate (di-*tert*-butyl pyrocarbonate) was obtained from Lancaster Synthesis, Inc. (97%, catalog no. 3289) as a white, frozen melt and was stored under refrigeration at 0-5 °C.

The melting ranges (thaw point to melting point) of organic solids used in this research project are compared with literature values in Table II, which also includes the solvent from which they were recrystallized repeatedly to an unchanged melting point. Aldrich Chemical Company, Inc. supplied hydroquinone (99%, catalog no. H1,790-2), *tert*-butylhydroquinone (97%, catalog no. 11,294-1), 2,5-di-*tert*-butylhydroquinone (99%, catalog no. 11,297-6), and 2,6-di-*tert*-butyl-1,4-benzoquinone (98%, catalog no. 15,393-1). The 1,4-benzoquinone was extracted from a practical grade sample of J. T. Baker Chemical Company (catalog no. B915)

Table II

Melting Ranges of Organic Solids and Their Recrystallizing Solvents

Compound	Recrystallizing Solvent	Experimental (uncorrected), °C	Literature Melting Point, °C	References
1,4-benzoquinone	diethyl ether	112.0-113.0	113	141, 142
<i>t</i> -butyl-1,4-benzoquinone	<i>n</i> -pentane	56.6- 57.9	59	140, 143
<i>t</i> -butylhydroquinone	toluene	127.9-128.5	128	1, 144
2,5-di- <i>t</i> -butyl-1,4-benzoquinone	hexanes	152.0-153.1	153	140, 143
2,6-di- <i>t</i> -butyl-1,4-benzoquinone	none	66.3- 68.0	68	144, 145
2,5-di- <i>t</i> -butylhydroquinone	toluene	215.7-217.8	219	1, 146
hydroquinone	abs ethanol	172.0-172.8	172	147, 148

with an insufficient amount of refluxing diethyl ether, then was recrystallized repeatedly until golden yellow, elongated prisms were obtained.

The *tert*-butyl-1,4-benzoquinone and 2,5-di-*tert*-butyl-1,4-benzoquinone were prepared through the oxidation of their hydroquinones with ceric ammonium nitrate supported 20 wt % on silica gel.¹⁴⁰ Fisher Scientific supplied the ceric ammonium nitrate (99.3%, catalog no. C-248) in ACS reagent grade, and the silica gel was obtained from the J. T. Baker Chemical Company (catalog no. 3404) as a 40-140 mesh powder. It should be noted that the silica gel used in this oxidation reaction was not the same as the silica gel employed in the Friedel-Crafts alkylation reaction.

Methods

Melting points are uncorrected and were determined under an atmosphere of dry nitrogen with a Thomas-Hoover oil-immersion Uni-Melt apparatus of the Arthur H. Thomas Company (Thomas Scientific no. 6427-K10) equipped with a transformer to control a Nichrome heater coil that is immersed in an illuminated, magnified, and mechanically stirred bath of silicone oil housed in a totally enclosed cabinet. The armored thermometer is encased in a glass sheath and is readable to 0.1 °C when it is magnified two times with an illuminated periscope accessory. In this configuration, a thermometer cannot be described as being

either partial or total immersion. Samples were ground to a powder with an agate mortar and pestle and dried in a vacuum desiccator at aspirator pressure over a mixture of anhydrous calcium chloride and indicating Drierite for a half hour, then were placed in oven-dried, borosilicate glass capillaries (Thomas Scientific catalog no. 6418-F10) of 110 mm length, 0.9 to 1.1 mm inside diameter, and about 0.25 mm wall thickness. After packing the sample tightly by dropping it 90 cm through a glass tube several times, the capillary was flushed 2 min with dry nitrogen and sealed with a flame. The flushing was continued during the sealing of the capillary and was accomplished by inserting a hypodermic needle attached to a nitrogen tank with clear PVC tubing and fastened with wire.

The boiling point reported for distilled liquids is that of the constant-boiling, middle fraction collected during the final distillation of each sample. These were recorded from a thermometer readable to 0.1 °C, which was calibrated for partial immersion to either 25 or 75 mm depth as was appropriate for the particular distilling head employed. The atmospheric pressure during the collection of this fraction is the mean of successive measurements made with a mercurial barometer from Princo Instruments, Inc. (Princo catalog no. D453). The barometer had a brass scale readable to 0.1 mmHg from a sliding vernier adjusted with a rack and pinion, a thermometer readable to 0.1 °C

attached to the metal housing of the glass barometer tube (6.4-mm bore), and a Fortin-type cistern for adjustment of the mercury pool to the zero reference point. Capillary correction of the mercury meniscus was taken into account in the manufacturer's calibration of the scale. Other barometric corrections¹⁴⁹ for temperature and gravity were made using standard tables¹⁵⁰ for local 35° 52' latitude and 187 m elevation, as supplied by Murfreesboro Municipal Airport.

Most reactions were conducted in a heavy-wall, 15-mL pressure tube of borosilicate glass obtained from Ace Glass Incorporated (catalog no. 8648-75) and equipped with a plunger valve. The stem of the plunger valve was inserted through the central hole of a Teflon bushing, which screws into the threaded top of the pressure tube. The body of the plunger valve could be positioned by means of a tight-fitting FETFE O-ring that permits purging and subsequent sealing of the charged pressure tube. This pressure tube provided a completely closed system and exhibited no loss of mass after heating the reaction mixture at 70 °C for 24 hours.

Reactions were conducted under an unbroken atmosphere of dry nitrogen through use of the plunger valve together with the apparatus described by Johnson and Schneider,¹⁵¹ which allowed evacuation to aspirator pressure and return to a pressure of one atmosphere of pure nitrogen by merely

turning a connecting stopcock. The nitrogen was obtained from MG Industries, Gas Products Division, in ultra high purity grade (99.999% minimum purity). It was passed through two 16 x 152 mm polyethylene drying tubes, one containing indicating Drierite (10-20 mesh) and the other containing activated coconut charcoal (8-12 mesh), on route to the reaction vessel.

In a typical experiment, a wide-stem powder funnel was placed in the neck of the pressure tube containing 1.00 g of Wakogel C-300 and a magnetic stir bar, then 0.22 g (2.0 mmol) of hydroquinone and 0.95 g (9.0 mmol) of anhydrous sodium carbonate were weighed separately on a square of creased aluminum foil and added to the tube. The sodium carbonate was finely powdered by grinding 4-5 min with an agate mortar and pestle immediately preceding weighing. The Wakogel C-300 had been previously weighed and dried while in the pressure tube by heating for a minimum of five hours at 170 ± 2 °C (4 ± 1 mmHg), then was cooled for one-half hour in a desiccator over anhydrous calcium chloride containing some indicating Drierite. After the solids were added to the pressure tube, 0.82 g (6.0 mmol) of *tert*-butyl bromide or 0.56 g (6.0 mmol) of *tert*-butyl chloride was weighed in a 5-mL centrifuge tube and transferred to the reaction mixture with a disposable Pasteur pipet. Then 7.0 ± 0.1 mL of carbon tetrachloride was measured with a 10-mL graduated cylinder and used to wash any material from the

centrifuge tube, aluminum foil, and filling funnel into the reaction mixture. The Teflon bushing, plunger valve, and O-ring assembly was screwed into the pressure tube and hand tightened. After the chemical system was thoroughly mixed for 1 min by magnetic stirring, the stem of the plunger valve was attached to the nitrogen/aspirator system with vacuum tubing, and the reaction mixture was purged a minimum of ten times with dry nitrogen. The charged and purged pressure tube was placed in a 10 x 10 cm Instatherm oil bath (Ace Glass no. 9603-20) containing low-temperature silicon oil (Ace Glass no. 14115-05, 180 °C maximum), which was mechanically stirred. A time-proportional, digital temperature controller (Ace Glass no. 12106-40) having a platinum sensor provided a long-term temperature stability of ± 0.3 °C, as monitored with a -20 to 110 °C partial immersion thermometer (Fisher 14-985B). Trial and error demonstrated that the most reliable magnetic stirring of the reaction mixture was accomplished by a 7.9 x 13 mm octagonal stir bar (Fisher Scientific no. 14-511-62) and a powerful Thermolyne model SPA-1025B stirrer/hot plate. A heavy, polycarbonate safety shield was kept in place while heating the closed system.

Some alkylation reactions were conducted with Kontes microflex microscale glassware having borosilicate glass components and polypropylene/PTFE threaded connectors. The reactor was composed of a 25-mL round-bottom flask attached

to a water-jacketed condenser and capped with a 100-mm air condenser/chromatography column to complete the assembly. Antifreeze was pumped through the condenser with a Haake F4291 circulator from a Haake K41 bath at a predetermined temperature and was monitored with a -50 to 50 °C low-temperature, partial immersion thermometer (Fisher 15-030) installed downstream from the condenser. A hose connector was employed to connect the 100-mm column to a drying tube containing indicating Drierite for reactions conducted open to the atmosphere. For isobutene-entrapment experiments, activated coconut charcoal (8-12 mesh) was poured into the 100-mm column and held in place by two 13-mm PTFE filter supports inserted at either end. The packed 100-mm column was dried at 170 ± 2 °C under a pressure of 4 ± 1 mmHg in a vacuum oven concurrently with the Wakogel C-300. Other isobutene-entrapment experiments were conducted under an atmosphere of dry nitrogen accomplished by purging the entire reaction system, then attaching a helium-quality balloon filled with nitrogen to the 100-mm column. In practice, this was most conveniently done by fitting the balloon to a shorter, 50-mm column, which could then be attached to either the nitrogen tank or the 100-mm column with threaded connectors.

Following the typical reaction time of 24 hours, the pressure tube was removed from the bath and cooled to room temperature with magnetic stirring for one-half hour, then

3.3 mL of acetone- d_6 was added. The reaction mixture was subsequently stirred for an additional 2-3 min and gravity filtered. The acetone- d_6 not only provides the deuterium lock for recording subsequent NMR spectra, but was also added here to render the many components of the reaction mixture more soluble. In this manner, solutions of various reaction mixtures in carbon tetrachloride diluted 30 v/v % with acetone- d_6 were prepared for recording their ^1H NMR spectra. In some early experiments, reaction mixtures were cooled to ice-bath temperature, but this was discontinued when precipitation of organic products was observed.

The presence of the solutes hydroquinone (2.0 mmol) and *tert*-butyl bromide (6.0 mmol) in the original 7.0 mL of pure carbon tetrachloride solvent caused a slight increase in total volume of the reaction mixture to 7.8 ± 0.1 mL. Consequently, $(0.30)(7.8 \text{ mL}) / (0.70 \text{ mL}) = 3.3$ mL of acetone- d_6 must be added for its concentration in the solution to be 30 v/v %. The maximum concentration of hydroquinone, and the products derived from hydroquinone, in the solution of the reaction mixture diluted 30% with acetone- d_6 cannot exceed $(2.0 \text{ mmol}) / (11.1 \text{ mL}) = 0.18 \text{ M}$. Similarly, the maximum concentration of *tert*-butyl bromide, and products derived from *tert*-butyl bromide, could be no more than $(6.0 \text{ mmol}) / (11.1 \text{ mL}) = 0.54 \text{ M}$. The ^1H NMR spectra of individual reference compounds were recorded from 0.19 M solutions in carbon tetrachloride containing 1 vol % of

tetramethylsilane and 30 vol % of acetone- d_6 . The final chemical shifts (δ) and proton integrations are reported in Tables III and V, respectively, of Chapter 3. These results are the mean values from at least four and in most cases five or six spectra recorded on different days from separate solutions, the preparation details of which are summarized in Table IV of Chapter 3.

Proton nuclear magnetic resonance (^1H NMR) spectra were taken at ambient probe temperatures of 296 ± 1 K from a 200 MHz Bruker AC 200 Fourier transform NMR spectrometer operating at an applied magnetic field, B_0 , of 4.701 T and calibrated to 200.133 MHz, the resonance frequency for protons. The NMR spectrometer was outfitted with a 5-mm broadband probe (14 MHz to 90 MHz). Data analysis and manipulation were conducted using an Aspect 3000 computer (with coprocessor), which is part of the Bruker AC 200 FT-NMR instrument. The program DISNMR 89 was the applications software.¹⁵²

Typically, NMR samples were set to spin at 20 rps and were subjected to 16 radio frequency pulses with a 30.0 s relaxation delay between pulses. Other initial acquisition parameters include: acquisition time of 3.408 s; frequency offset of 4400 Hz; synthesizer frequency of 80.030 Hz; and pulse width of 2.0-2.5 μs . Most free induction decays were collected using a data array, SI, of 16K (i.e., SI = 16,384 data points) and a sweep width, SW, of 2403.846 Hz, which

provide a digital resolution of $2(SW/SI) = 0.293$ Hz per data point for routine spectra.¹⁵³ Higher resolution was obtained by increasing SI from 16K to any other integral multiple of eight, with data arrays of 64K and 128K being the most commonly selected for the high resolution needed to resolve closely spaced multiplets. Increasing the data array to 64K results in the collection of 65,536 data points to afford an increased resolution of 0.073 Hz per data point if the sweep width remains unchanged.

The Wilmad Glass Company, Inc. supplied Pyrex 5-mm NMR tubes (catalog no. 507-PP) fitted with Teflon caps (catalog no. WG-1264-5) having a maximum concentricity of 51μ , 4.97 ± 0.01 mm OD, and 4.20 ± 0.01 mm ID. The NMR tubes, Teflon caps, Pasteur pipets, and all other glassware employed in solution preparation were soaked overnight in a 2% NRS-250 surfactant solution from Norell, Inc., then were rinsed with copious amounts of water followed by 95% ethanol and stored in a radiation-conduction-type laboratory oven at 135 ± 3 °C. When needed, glassware was removed from the oven, cooled for one hour in a desiccator over anhydrous calcium chloride containing some indicating Drierite, and used at once. This precaution minimizes the condensation of water and adsorption of organic materials from air onto the surface of glass.¹⁵⁴

CHAPTER 3

Results and Discussion

NMR Spectra of Reference Compounds

A technique was sought to identify and to quantify the products and byproducts produced during the Friedel-Crafts alkylation of hydroquinone with *tert*-butyl bromide, which was conducted by stirring a carbon tetrachloride solution over a mixture of silica gel and powdered sodium carbonate for 24 hours at 70 °C according to the procedure of Hojo.¹ This reaction was previously discussed in Chapter 1 and is illustrated in Figure 1 on page 8. The results presented here are part of a continuing study¹⁵⁵ that is directed towards providing a better understanding of the role played by silica gel as the acidic catalyst in the mechanism of this and related⁷³ heterogeneous reactions. The methods of both HPLC and GC, which are often employed in organic trace analysis,¹⁵⁶⁻¹⁵⁹ were tried; however, these were discarded early in the project because they were unsuccessful, in our hands, in resolving all components of the reaction mixture in a single chromatogram. Additionally, chromatographic conditions were not found that prevented further, undesired reaction of some of the more unstable components. Proton NMR was next investigated as a possible analytical method, one which subsequently satisfied all of our needs.

Many products are possible in this reaction mixture, and the most probable of these derived from hydroquinone are summarized in Figure 2. Friedel-Crafts alkylation can produce *tert*-butylhydroquinone and both 2,5- and 2,6-di-*tert*-butylhydroquinone. Therefore, an excess of *tert*-butyl bromide was employed to insure that di-*tert*-butylation is essentially complete, yielding almost exclusively the less sterically hindered 2,5-di-*tert*-butylhydroquinone. This is also the result for reactions conducted under homogeneous conditions.^{60,160-165} Each of the hydroquinones¹⁴⁷ can be oxidized¹⁶⁶⁻¹⁶⁸ to its corresponding 1,4-benzoquinone¹⁴² or O-alkylated^{61,62} on either or both of its hydroxyl groups; however, the latter products could also undergo a phenolic ether rearrangement⁶³ of *tert*-butyl groups from oxygen to the aromatic ring. Figure 3 shows possible products that could be derived from the *tert*-butyl bromide alkylating agent. Elimination can afford isobutene (2-methylpropene) and subsequent isobutene dimers 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene¹⁶⁹⁻¹⁷¹ or the saturated 2,2,4-trimethylpentane¹⁵ under conditions where hydride abstraction is possible. Di-*tert*-butyl ether may be yet another possible byproduct, which is produced through the intermediacy of di-*tert*-butyl carbonate according to the mechanistic proposal of Olah.¹⁷²

The proton NMR spectra of sixteen reference compounds that were used to either identify or disprove the presence

of components in the reaction mixture are summarized in Table III and were recorded with a 200 MHz Bruker AC 200 Fourier transform nuclear magnetic resonance spectrometer from solutions whose composition is found in Table IV. Spectra for both the reference compounds and the reaction mixture were recorded from samples dissolved in carbon tetrachloride containing 30 vol % of acetone- d_6 to provide the deuterium lock signal and a minimal 1 vol % of TMS (tetramethylsilane) to serve as an internal reference for chemical shift. It should be noted that *tert*-butyl methyl ether and di-*tert*-butyl dicarbonate were used as model compounds to approximate the *tert*-butyl chemical shifts of the commercially unavailable di-*tert*-butyl ether and di-*tert*-butyl carbonate, respectively.

The uncertainty given for each chemical shift in Table III is the standard deviation obtained from the mean of at least four and in most cases five or six spectra recorded on different days and from separately prepared solutions. These standard deviations demonstrate that the numerical values for the chemical shifts of nonexchangeable protons were reproducible to the fourth decimal place if a small correction was uniformly added to or subtracted from the observed chemical shifts when a nonzero value for the tetramethylsilane internal reference appeared in the peak table. The following criteria were imposed upon the set of spectra acquired for the reference compounds to insure

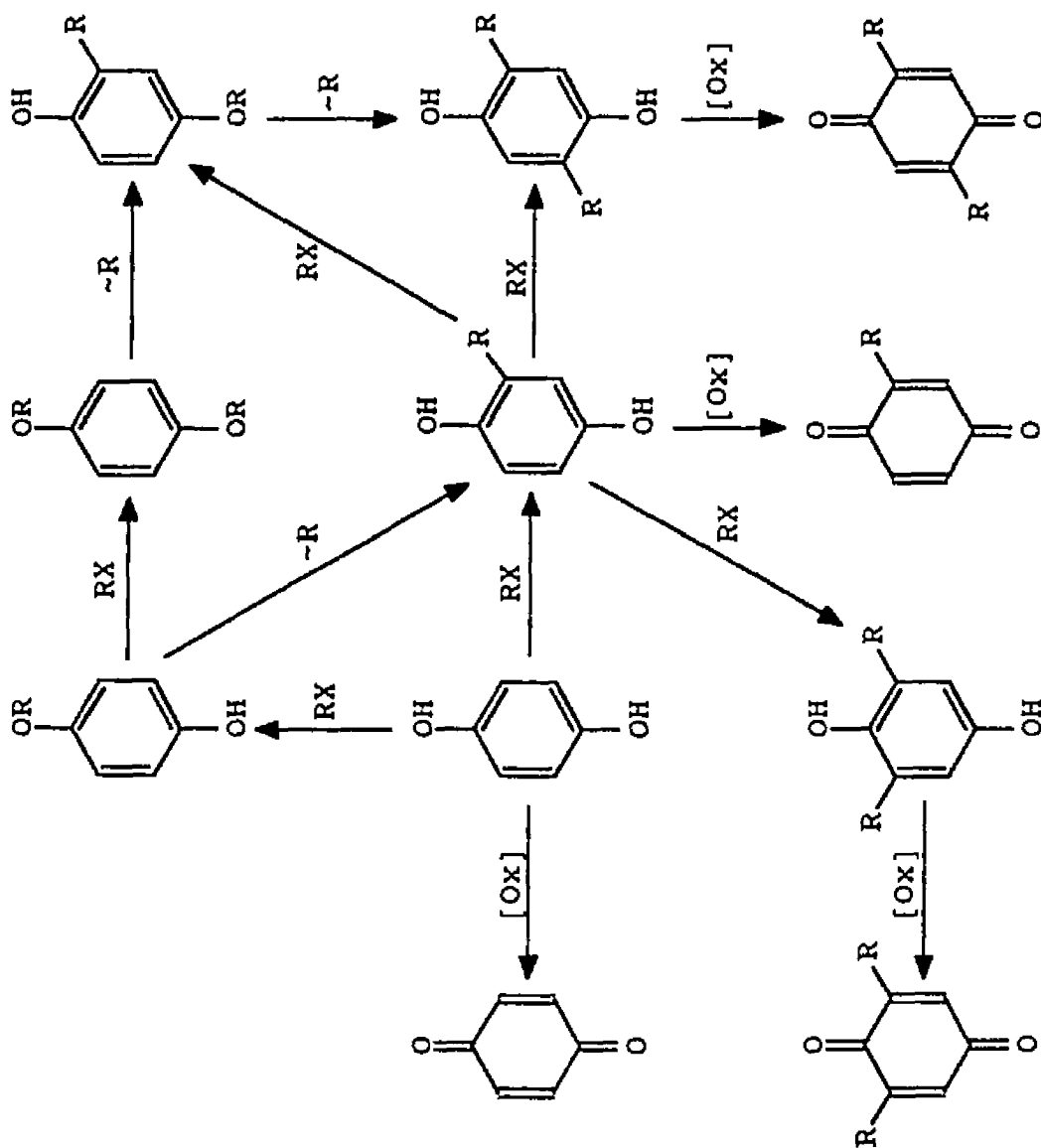


FIGURE 2. Possible Reaction Mixture Components Formed from Hydroquinone.

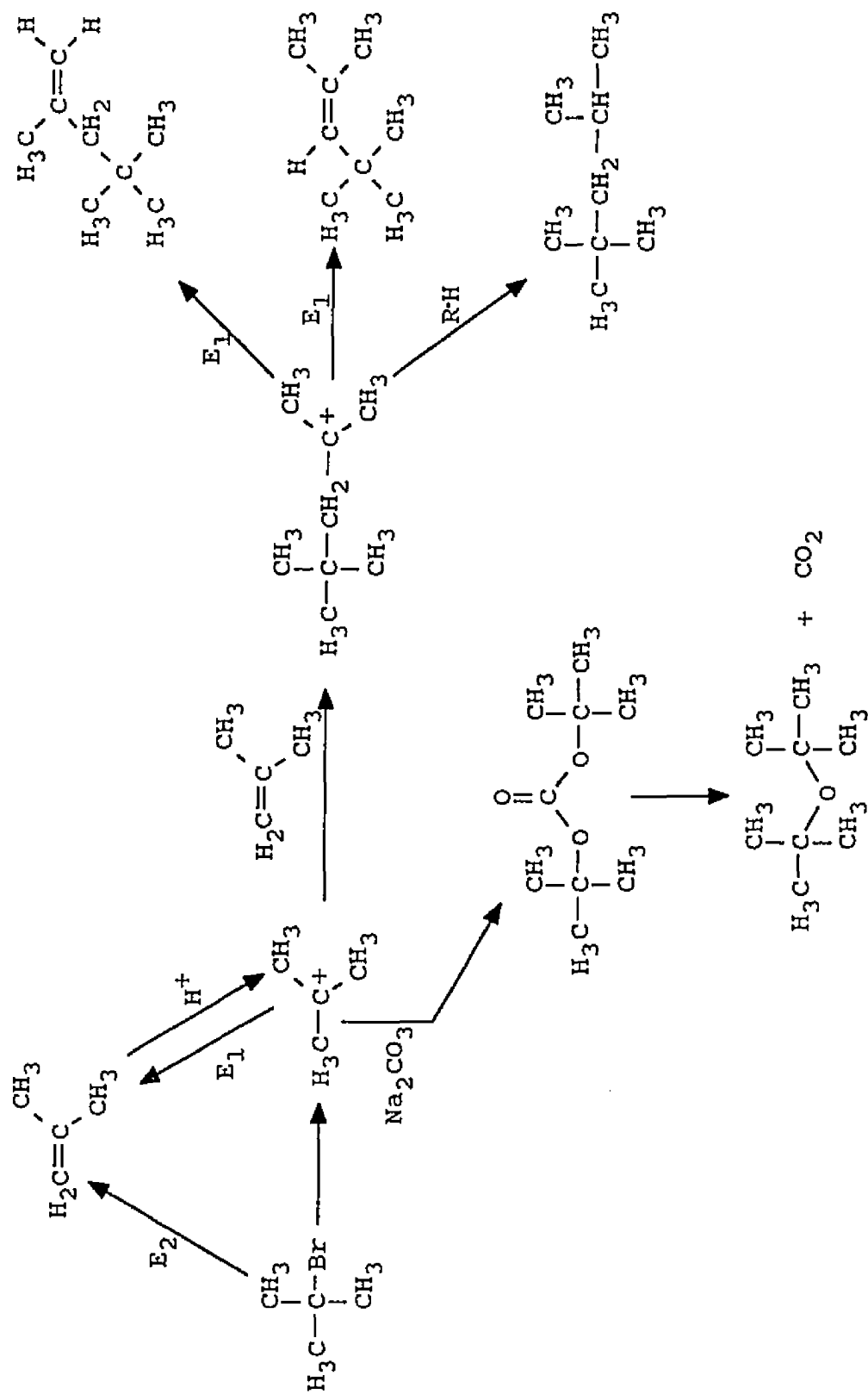


FIGURE 3. Possible Reaction Mixture Components Formed from tert-Butyl Bromide.

Table III

¹H NMR Spectra^a for Carbon Tetrachloride Solutions Containing 30% Acetone-d₆

Compound	Molarity, Chemical Shifts, Multiplicity, and Integration	
	mol/L	δ in ppm
1,4-benzoquinone	0.19	6.7721 ± 0.0007 (s)
t-butyl alcohol	0.54	1.1744 ± 0.0002 (s, 9.0 H), 2.90 ± 0.01 (s, 1.0 H)
	0.19	1.1718 ± 0.0002 (s, 9.0 H), 2.73 ± 0.01 (s, 1.0 H)
t-butyl bromide	0.54	1.7877 ± 0.0003 (s)
	0.19	1.7888 ± 0.0001 (s)
t-butyl-1,4-benzoquinone	0.19	1.2875 ± 0.0001 (s, 9.0 H), 6.511 ± 0.001 (d of d, 1.0 H _C), 6.669 ± 0.003 (d, J _{AC} = 1.5 ± 0.1 and J _{AB} ~ 0 Hz, 1.0 H _A), 6.671 ± 0.003 (d, J _{BC} = 0.9 ± 0.1 and J _{AB} ~ 0 Hz, 1.0 H _B)
t-butyl chloride	0.54	1.6042 ± 0.0002 (s)
	0.19	1.6049 ± 0.0001 (s)

^aAll coupling constants were derived from multiplet spacings through first-order analysis only. The uncertainty given for chemical shifts and coupling constants is the standard deviation obtained from the mean of at least four spectra. Thus, it is a measure of precision and not absolute accuracy.

Table III (continued)

Compound	Molarity, Chemical Shifts, Multiplicity, and Integration	
	mol/L	δ in ppm
<i>t</i> -butylhydroquinone	0.19	1.3461 \pm 0.0002 (s, 9.0 H), 6.3774 \pm 0.0005 (d of d, 1.0 H _C), 6.5168 \pm 0.0008 (d, J _{AC} = 8.43 \pm 0.01 and J _{AB} \sim 0 Hz, 1.0 H _A), 6.6370 \pm 0.0005 (d, J _{BC} = 2.89 \pm 0.01 and J _{AB} \sim 0 Hz, 1.0 H _B), 7.10 \pm 0.01 (s, 1.0 H), ^b 7.24 \pm 0.01 (s, 1.0 H) ^b
<i>t</i> -butyl methyl ether	0.54	1.1222 \pm 0.0001 (s, 9.0 H), 3.1051 \pm 0.0002 (s, 3.0 H)
	0.19	1.1223 \pm 0.0001 (s, 9.0 H), 3.1047 \pm 0.0002 (s, 3.0 H)
2,5-di- <i>t</i> -butyl-1,4-benzoquinone	0.19	1.2685 \pm 0.0001 (s, 18.0 H), 6.4128 \pm 0.0011 (s, 2.0 H)
2,6-di- <i>t</i> -butyl-1,4-benzoquinone	0.19	1.2916 \pm 0.0001 (s, 18.0 H), 6.4230 \pm 0.0005 (s, 2.0 H)
di- <i>t</i> -butyl dicarbonate	0.19	1.5149 \pm 0.0003 (s)
2,5-di- <i>t</i> -butylhydroquinone	0.19	1.3157 \pm 0.0002 (s, 18.0 H), 6.562 \pm 0.001 (s, 2.0 H), 6.98 \pm 0.02 (s, 2.0 H) ^b

^bIdentified as hydroxyl by its chemical exchange with both D₂O and CF₃CO₂H.

Table III (continued)

Compound	Molarity, Chemical Shifts, Multiplicity, and Integration	
	mol/L	δ in ppm
2,6-di- <i>t</i> -butylhydroquinone	0.19	1.3785 \pm 0.0002 (s, 18.0 H), 5.01 \pm 0.02 (s, 1.0 H, C ₁ -OH), 6.557 \pm 0.002 (s, 2.0 H), 7.09 \pm 0.03 (s, 1.0 H, C ₄ -OH)
hydroquinone	0.19	6.5708 \pm 0.0009 (s, 4.0 H), 7.30 \pm 0.02 (s, 2.0 H)
2,2,4-trimethylpentane	0.54	0.8976 \pm 0.0002 (s, 9.0 H), 0.9112 \pm 0.0005 (d, J = 6.6 \pm 0.1 Hz, 6.0 H), 1.1286 \pm 0.0003 (d, J = 5.4 \pm 0.1 Hz, 2.0 H), centered 1.6685 \pm 0.0005 (m, 1.0 H)
2,4,4-trimethyl-1-pentene	0.54	0.9257 \pm 0.0001 (s, 9.0 H), 1.7614 \pm 0.0003 (d of d, J = 1.5 \pm 0.1 and 0.8 \pm 0.1 Hz, 3.0 H), 1.9216 \pm 0.0004 (d, J = 0.7 \pm 0.1 Hz, 2.0 H), 4.5912 \pm 0.0003 (m, 1.0 H), 4.7953 \pm 0.0003 (m, 1.0 H)
2,4,4-trimethyl-2-pentene	0.54	1.0768 \pm 0.0001 (s, 9.0 H), 1.6385 \pm 0.0002 (d, J = 1.4 \pm 0.1 Hz, 3.0 H), 1.7011 \pm 0.0002 (d, J = 1.3 \pm 0.1 Hz, 3.0 H), centered 5.1173 \pm 0.0004 (apparent heptet, 1.0 H)

Table IV

Composition of ^1H NMR CCl_4 Solutions Containing 30% Acetone- d_6

Compound	M_r , ¹⁷³ g/mol	Mass, g	Volume			M, mol/L	w/v %, g/100 mL
			CCl_4 , mL	$(\text{CD}_3)\text{CO}$, mL	Total, mL		
1,4-benzoquinone	108.097	0.22	7.2	3.2	10.6	0.19	2.1
t-butyl alcohol	74.123	0.44	7.0	3.3	11.0	0.54	4.0
		0.15	7.2	3.2	10.5	0.19	1.4
t-butyl bromide	137.020	0.82	7.0	3.3	11.0	0.54	7.5
		0.27	7.1	3.1	10.4	0.19	2.6
t-butyl-1,4-benzoquinone	164.204	0.33	7.0	3.1	10.5	0.19	3.1
t-butyl chloride	92.568	0.55	7.0	3.3	10.9	0.54	5.0
		0.19	7.2	3.2	10.7	0.19	1.8
t-butylhydroquinone	166.220	0.33	7.0	3.2	10.4	0.19	3.2

Table IV (continued)

Compound	M_r , ¹⁷³ g/mol	Mass, g	Volume			M , mol/L	w/v %, g/100 mL
			CCl_4 , mL	$(CD_3)CO$, mL	Total, mL		
<i>t</i> -butyl methyl ether	88.150	0.53	7.0	3.3	11.1	0.54	4.8
		0.18	7.1	3.2	10.5	0.19	1.7
2,5-di- <i>t</i> -butyl-1,4-benzoquinone	220.312	0.44	7.0	3.2	10.6	0.19	4.2
2,6-di- <i>t</i> -butyl-1,4-benzoquinone	220.312	0.44	7.0	3.2	10.6	0.19	4.2
di- <i>t</i> -butyl dicarbonate	218.250	0.44	7.0	3.2	10.6	0.19	4.2
2,5-di- <i>t</i> -butylhydroquinone	222.328	0.44	7.0	3.2	10.5	0.19	4.2
2,6-di- <i>t</i> -butylhydroquinone	222.328	0.44	7.0	3.2	10.6	0.19	4.2
hydroquinone	110.112	0.22	7.1	3.1	10.3	0.19	2.1
2,2,4-trimethylpentane	114.231	0.68	6.9	3.3	11.1	0.54	6.1
2,4,4-trimethyl-1-pentene	112.215	0.67	6.9	3.3	11.1	0.54	6.0
2,4,4-trimethyl-2-pentene	112.215	0.67	6.9	3.3	11.1	0.54	6.0

that the chemical shifts and spin-spin coupling constants reported here are accurate and reproducible:

1. The NMR spectra of pure compounds were recorded in the same solvent that was used to acquire the spectrum of the reaction mixture.
2. The final chemical shifts and coupling constants are the mean of at least four independent spectra obtained from separately prepared solutions.
3. All integrations must agree with the molecular formula within 0.1 hydrogen for each compound.
4. The standard deviation of the chemical shifts must not be limited by any variation in solution composition or concentration, but by instrumental precision alone.
5. A reasonable interpretation for all features of each NMR spectrum must be provided.

The initial spectra of *tert*-butyl alcohol and the various hydroquinones would not integrate properly. The integrated peak areas for the hydroxyl protons of these compounds were all low by the same proportional amount, which was caused by chemical exchange with D_2O introduced as an impurity into the acetone- d_6 solvent. Careful integration of the original spectra obtained from *tert*-butyl alcohol, hydroquinone, *tert*-butylhydroquinone, and 2,5-di-*tert*-butylhydroquinone were all consistent with a nearly 0.4 M concentration of D_2O in a sample of acetone- d_6 that was stored over 4A molecular sieve for several months. An explanation for this contamination is shown in Figure 4. Here, molecular sieve is proposed to catalyze enolization,

aldol condensation, and subsequent elimination to form one mole of fully deuterated mesityl oxide and one mole of D_2O for every two moles of acetone- d_6 consumed. An analogous process has already been described in the literature for undeuterated acetone,¹⁷⁴ which has been studied extensively as a preparative method.^{88,175} The self-condensation of acetone- d_6 stored over 4A molecular sieve is especially detrimental here because the formation of the deuterated products were undetected by proton NMR. Thus, an erroneous opinion concerning the purity and even the composition of the solvent resulted.¹⁷⁶ Consequently, all of our early spectra were discarded and were reacquired from solutions prepared using fresh, uncontaminated batches of acetone- d_6 .

The major conclusion of this project is that 1H NMR spectra of the sixteen reference compounds studied are all sufficiently different to allow their identification and quantification in the mixture of products and byproducts produced during the Friedel-Crafts *tert*-butylation of hydroquinone with *tert*-butyl bromide. Identification of components in the 1H NMR spectrum of the reaction mixture was successful largely because the *tert*-butyl group, which is part of the structure of fourteen of these compounds, exhibited a δ 0.9-1.8 range in chemical shift. A very similar range of δ 0.8-1.9 was reported for 57 *tert*-butyl derivatives by Wilk et. al.,¹⁷⁷ who estimated that solvent-solute interactions contribute as much as 0.04 ppm to the

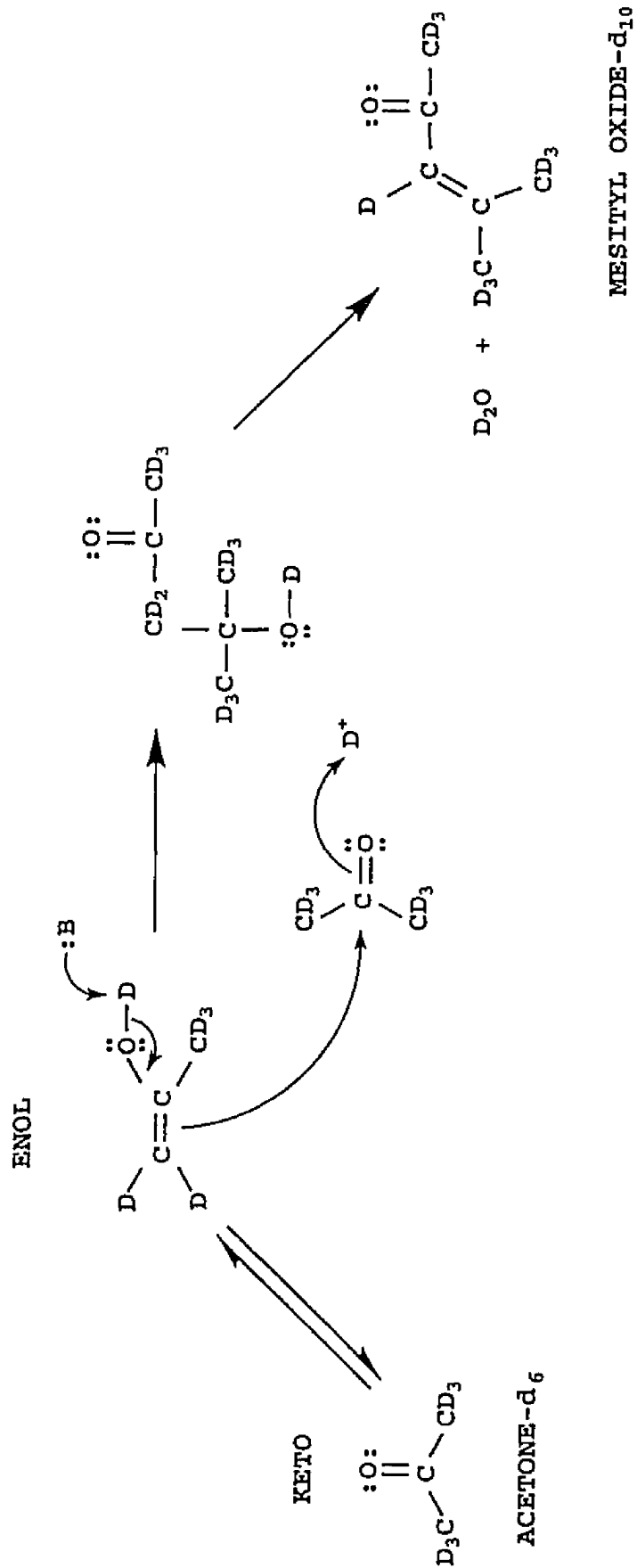


FIGURE 4. Aldol Condensation of Acetone-d₆ by 4A Molecular Sieve.

^1H chemical shift of a *tert*-butyl group when recorded in different solvents.

No correlation was found between the chemical shift of *tert*-butyl groups and the electronegativity of substituents attached to their quaternary carbon. There is, however, a roughly linear relationship between the chemical shift and the $^1\text{J}(^{13}\text{C},^1\text{H})$ heteronuclear spin-spin coupling constant of these protons with the natural abundance carbon-13 atoms in their methyl groups.¹⁷⁸⁻¹⁸⁰ The linear correlation is nearly exact if a consistent 0.16 ppm magnetic anisotropic effect is taken into account for aromatic ring currents (deshielding), the carbonyl groups of 1,4-benzoquinones (shielding), and the filled 3d subshell of bromine atoms (deshielding). This suggests that the magnitudes of both the *tert*-butyl ^1H chemical shift and $^1\text{J}(^{13}\text{C},^1\text{H})$ coupling constant are related to a common factor, the details of which have been reported elsewhere.^{181,182}

Analytical NMR

Although NMR spectroscopy is an analytical method in virtually all of its many applications, it is not commonly recognized as the instrument of choice for the quantitative trace analysis of multicomponent mixtures. This is partly because an NMR spectrometer is innately less sensitive than most other analytical instruments and partly because it is so versatile that other applications eclipse its analytical

potential.¹⁸³ The use of NMR in analytical chemistry was hesitant, being limited by the accessibility of commercial instruments whose performance would meet the requirements for this type of work;¹⁸⁴ however, the basic principles of analytical NMR were proposed and elaborated by the pioneers of the field,¹⁸⁵⁻¹⁸⁷ including the very influential book of Leyden and Cox,¹⁸⁸ and are now being increasingly exploited as a result of the increased sensitivity attainable from high-field, Fourier transform NMR spectrometers.¹⁸⁹⁻¹⁹²

The relative intensities of a set of NMR signals are more accurately measured by their areas rather than their peak heights because the line shapes can be broadened from a Lorentzian to a Gaussian distribution by both internal and external factors¹⁹³ including spin-lattice and spin-spin relaxation times, nuclear quadrupole moments, any inhomogeneity of the magnetic field, and dynamic phenomena.

NMR spectroscopy has a very important advantage over chromatographic and other spectroscopic methods in that the integrated intensity of each absorption is proportional to the concentration of the nuclei that created it, which means that the relative intensities are independent of the chemical nature of a given isotopic nucleus and can be converted directly to mole percentages without the need of chromatographic detector response factors or spectroscopic molar absorptivity (extinction coefficient).¹⁹⁴ The width of NMR resonances are usually narrow relative to the

chemical shift differences, which reduces the chance that various components of a mixture will have overlapping peaks in their composite spectrum. Furthermore, chemical shifts, multiplicities, and coupling constants can be employed, together with the integrated proton ratios, to elucidate the chemical structure of unknown components in a complex mixture.^{195,196}

Accurate determination of the percentage composition of a mixture requires that an assignment of a peak or peaks in the NMR spectrum be made for each individual component. Once the relative area of each peak has been measured and normalized with the number of protons known to be in the molecular structure for the chemical group associated with it, the mole percentages of all components can be obtained by straightforward calculations. The actual accuracy and reproducibility that is attained in the integration of NMR intensities depend on many factors including the condition and environment of the instrument, the absence of drift in the amplifying circuit, the signal-to-noise ratio, the quality of the phase correction, the resolution, and the absence of any saturation of the nuclear spin system being integrated. As with other physical measurements, accuracy and precision can be improved by averaging a number of replicate integrations.

A significant part of the present study involved the identification of components present in a reaction mixture

by comparison with the ^1H NMR spectra of sixteen reference compounds that are listed in Table III. The hydrogen atoms of these organic compounds are located in diverse chemical environments including alkyl, vinyl, and hydroxyl groups as well as being attached to benzene, hydroquinone, and 1,4-benzoquinone rings. Thirteen of the sixteen reference compounds contain more than one magnetically nonequivalent sets of protons, and, thus, they provide a measure of the accuracy and precision attainable upon integration of the relative areas of their resonances.

Table V provides a summary of the mean and standard deviation obtained for the electronic integration of each magnetically nonequivalent group of protons contained in all thirteen compounds along with the number of independent spectra whose integrations were averaged. The whole-number ratio of these integrations exhibited an average deviation of ± 0.014 H from the actual number of hydrogen atoms in the molecular formulas. Consequently, the accuracy is of the same magnitude as the typical ± 0.023 H standard deviation obtained by averaging replicate integrations from separate spectra. These standard deviations are plotted against the absolute hydrogen atom counts (i.e., 3 H for methyl, 18 H for *tert*-butyl, etc.) in Figure 5, which shows that the precision is constant and is not proportional to the area of the individual peaks. The accuracy and precision of normalized, peak-area ratios for different compounds in the

Table V

Accuracy and Precision of Replicate Integrations

Compound	Number of Integrations	Relative Number of Hydrogens		
		Alkyl	Vinyl/Aromatic	Hydroxyl
<i>t</i> -butyl alcohol (0.54 M)	4	9.026 ± 0.032		0.974 ± 0.032
<i>t</i> -butyl alcohol (0.19 M)	8	8.984 ± 0.033		1.016 ± 0.033
<i>t</i> -butyl-1,4-benzoquinone	5	9.018 ± 0.061	0.998 ± 0.036 0.992 ± 0.014 0.992 ± 0.014	
<i>t</i> -butylhydroquinone	6	9.057 ± 0.039	0.999 ± 0.008 1.004 ± 0.011 0.996 ± 0.008	0.982 ± 0.019 0.962 ± 0.016
<i>t</i> -butyl methyl ether (0.54 M)	5	8.982 ± 0.037 3.018 ± 0.037		
<i>t</i> -butyl methyl ether (0.19 M)	7	9.003 ± 0.021 2.997 ± 0.021		
2,5-di- <i>t</i> -butyl-1,4-benzoquinone	8	17.998 ± 0.023	2.002 ± 0.023	
2,6-di- <i>t</i> -butyl-1,4-benzoquinone	6	17.997 ± 0.029	2.003 ± 0.029	

Table V (continued)

Compound	Number of Integrations	Relative Number of Hydrogens		
		Alkyl	Vinyl/Aromatic	Hydroxyl
2,5-di- <i>t</i> -butylhydroquinone	4	17.996 ± 0.013	1.996 ± 0.010	2.008 ± 0.020
2,6-di- <i>t</i> -butylhydroquinone	5	18.009 ± 0.020	1.987 ± 0.017	1.008 ± 0.037 0.996 ± 0.042
hydroquinone	6		4.003 ± 0.018	1.997 ± 0.018
2,2,4-trimethylpentane	4	9.019 ± 0.026 6.014 ± 0.018 2.000 ± 0.003 0.967 ± 0.044		
2,4,4-trimethyl-1-pentene	4	9.044 ± 0.012 2.993 ± 0.010 1.975 ± 0.007	1.001 ± 0.006 0.987 ± 0.012	
2,4,4-trimethyl-2-pentene	4	9.025 ± 0.041 2.974 ± 0.016 2.974 ± 0.016	1.027 ± 0.020	

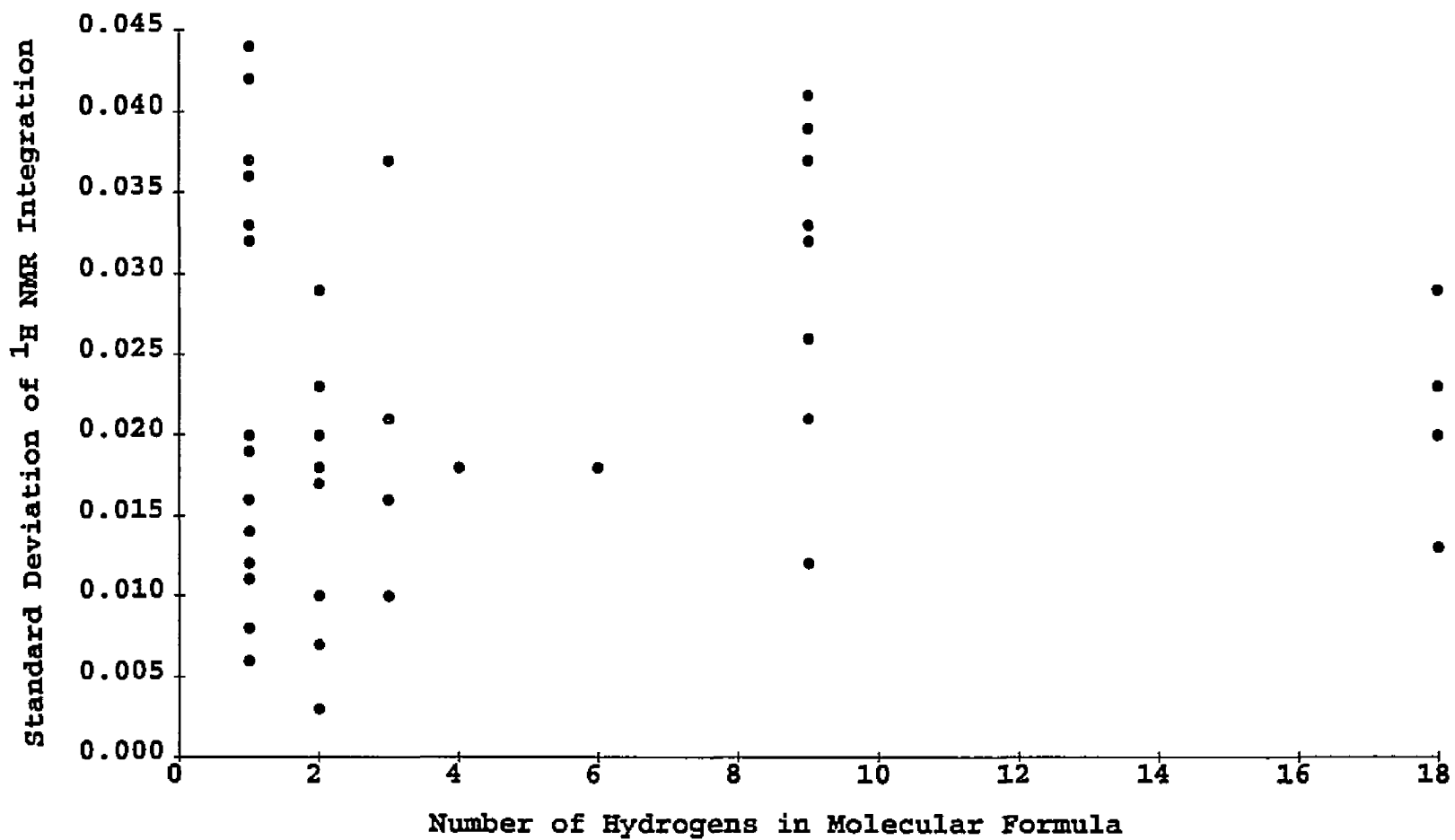


FIGURE 5. Precision of ^1H NMR Integration Compared with Absolute Hydrogen Count.

reaction mixture is expected to be the same as those described here for resonances from sets of magnetically nonequivalent protons contained within the same molecule.

NMR Spectrum of the Reaction Mixture

Friedel-Crafts *tert*-butylation of 1,4-hydroquinone (2.0 mmol) with excess *tert*-butyl bromide (6.0 mmol) gives 2,5-di-*tert*-butylhydroquinone of unusually high purity when a carbon tetrachloride solution (7.0 mL) is stirred under a nitrogen atmosphere for 24 hours at 70 °C in contact with solid silica gel (1.00 g, Wakogel C-300, dried 5 hours at 170 °C under vacuum) and powdered sodium carbonate (9.0 mmol). This is an example of the modified Friedel-Crafts procedure of Hojo,^{1,73} which employs silica gel as a mild and, therefore, selective Lewis acid catalyst. The mixture of minor byproducts produced in the *tert*-butylation reaction affords a complicated NMR spectrum with many peaks in the aromatic, olefinic, hydroxyl, and alkyl regions; however, the spectra of all significant components of the product distribution were discernible and most have now been identified. These assignments were made by comparison of the proton NMR spectrum of the reaction mixture with the spectra of the reference compounds previously summarized in Table III.

The NMR spectrum of the reaction mixture shows that the 2,5-di-*tert*-butylhydroquinone product and unreacted

tert-butyl bromide alkylating agent are the main components when the procedure is strictly followed. Under conditions of incomplete alkylation, the aromatic resonance of the hydroquinone starting material (δ 6.571) is also observed; however, adequate resolution of this singlet from that of the product (δ 6.562) is only achieved when a few drops of trifluoroacetic¹²³ acid has been added to the NMR sample as shown in Figure 6.

The main contributions of the present research were developing the methodology for running this reaction under exactly controlled conditions and identifying the other components of the reaction mixture. The equipment and rigorous procedures necessary to conduct this reaction in a controlled and reproducible manner for quantitative experiments were especially hard won and are described in detail in Chapter 2. Exact control of the temperature and uniform stirring of the heterogeneous mixture needed to be maintained for the entire reaction time of 24 hours. Air must be excluded from the reaction mixture and no leakage of volatile components from the closed system can occur, even for reaction at the reflux temperature of the carbon tetrachloride solvent. An example of the many experiments conducted to establish the final methodology is shown in Figure 7, which displays the ¹H NMR spectra of the aromatic region of reaction mixtures at various temperatures. The presence of the hydroquinone singlet shows that incomplete

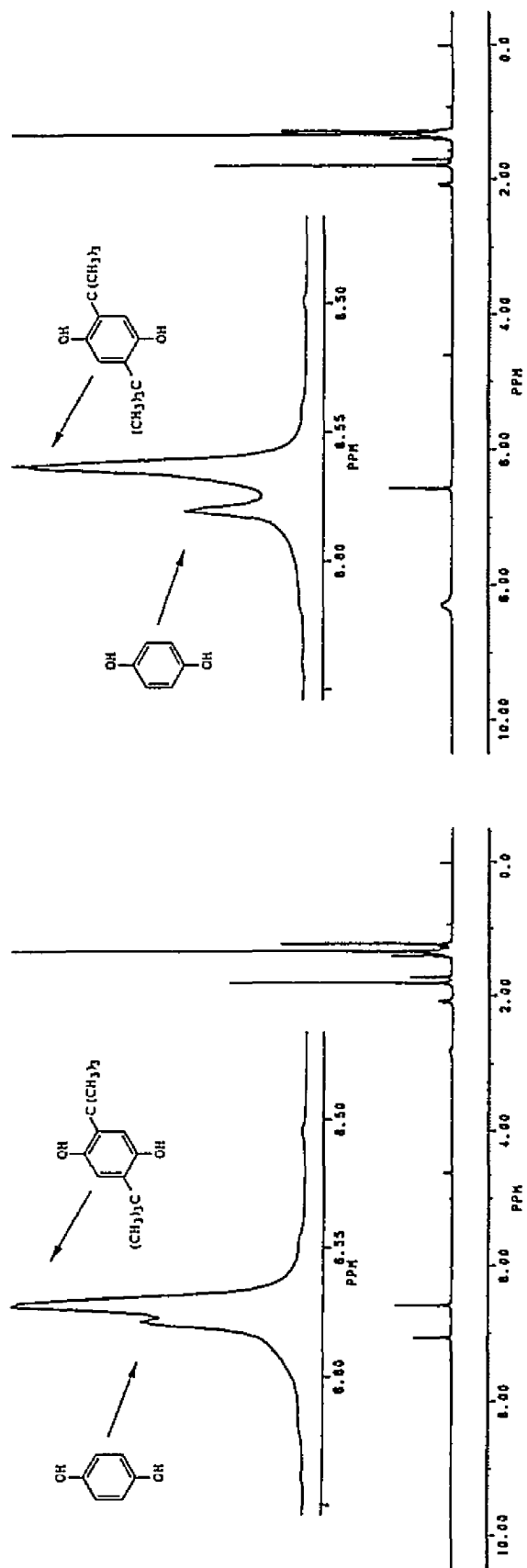


FIGURE 6. ^1H NMR Spectra of Partially Alkylated Product in the Absence (left) and Presence (right) of $\text{CF}_3\text{CO}_2\text{H}$.

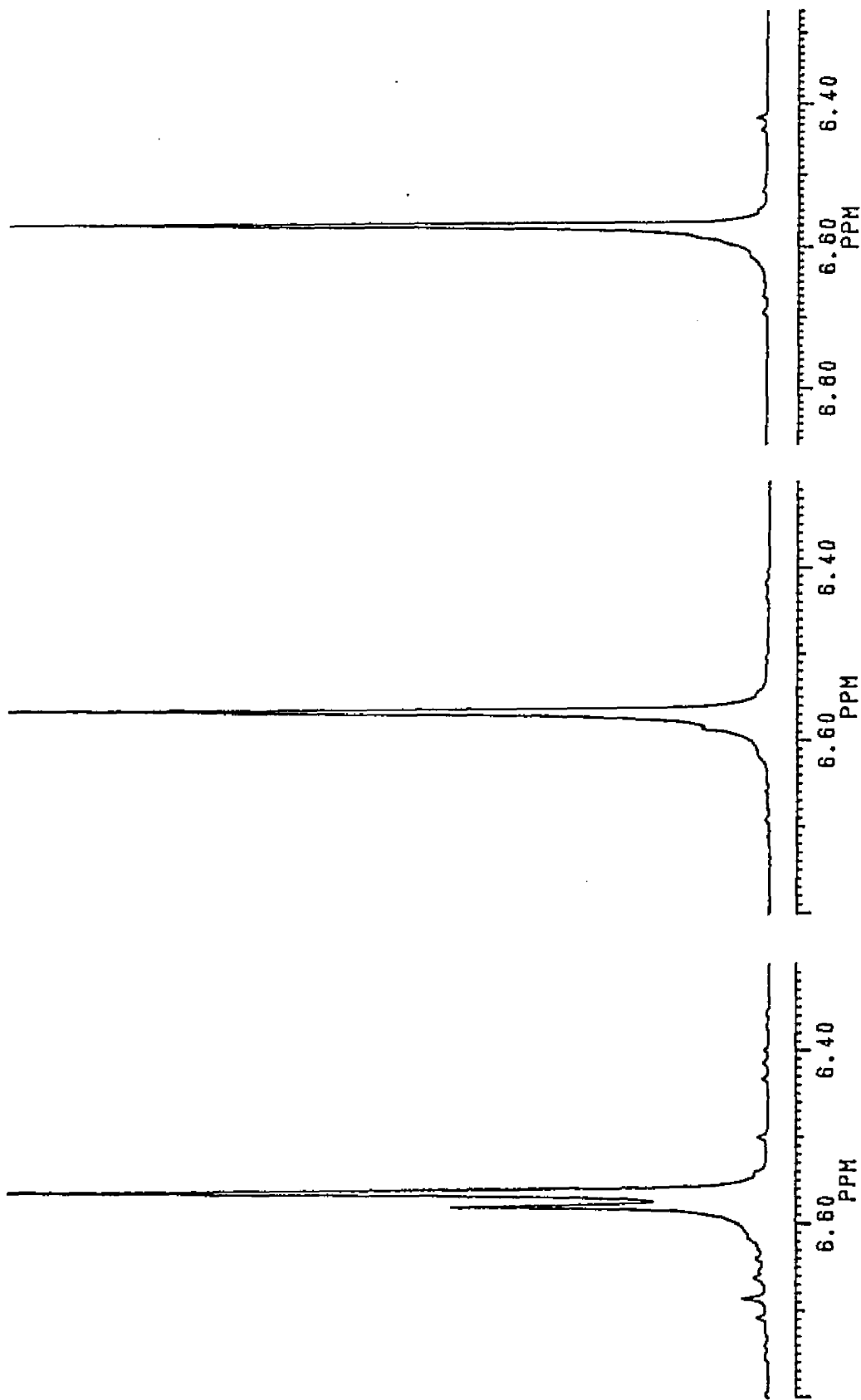


FIGURE 7. Comparison of ¹H NMR Spectra of Reaction Mixtures at 60, 70, and 80 °C, Respectively.

alkylation occurs when the reaction was conducted at 60 °C. A slight increase in product yield is apparent when the temperature was increased from 70 to 80 °C; however, the higher temperature also increases the amount of byproducts formed from the excess of *tert*-butyl bromide present during the course of the reaction. Thus, 70 °C was selected as the optimum reaction temperature.

Very minor amounts of other byproducts derived from hydroquinone are observed in the reaction mixture, the most prominent of which is 2,6-di-*tert*-butylhydroquinone and, to a much smaller extent, *tert*-butylhydroquinone. Only traces of 1,4-benzoquinone and 2,5-di-*tert*-butyl-1,4-benzoquinone could be detected when the reaction was conducted under an atmosphere of nitrogen. Other trace peaks grouped near the prominent *tert*-butyl resonance of the product are presently unidentified, but are suspected to be due to *tert*-butoxy groups resulting from O-alkylation of the hydroxyls of the various hydroquinones.

Small amounts of isobutene (2-methylpropene) and its olefinic dimers were also present. The oligomerization of isobutene and other olefins to yield a series of dimers, trimers, and higher homologs is an important process of the petroleum industry,¹⁵ and has been conducted in both homogeneous solution¹⁶⁹⁻¹⁷¹ and in heterogeneous reactions involving zeolites.^{79,197} The isobutene dimers 2,4,4-

trimethyl-2-pentene and 2,4,4-trimethyl-1-pentene were identified by their tert-butyl resonances at δ 1.077 and δ 0.926, respectively, and were confirmed by the chemical shifts and multiplicities of their other protons. These were formed from isobutene in the same 1:4 equilibrium ratio reported¹⁶⁹⁻¹⁷¹ for acidic homogeneous conditions, where the predominate product is the terminal olefin (disubstituted) and not the internal one (trisubstituted) anticipated from Sayteff's rule. The saturated 2,2,4-trimethylpentane dimer, however, was not detected and indicates that hydride transfer is not a viable option under these reaction conditions.

Isobutene was identified in the NMR spectrum of the reaction mixture by its distinctive spin-spin coupling pattern¹⁹⁸ composed of a six-hydrogen triplet in the alkyl region and a two-hydrogen heptet in the vinyl region as shown in Figure 8. The observation of isobutene in the reaction mixture suggests a mechanism in accord with proposals made for similar Friedel-Crafts alkylations.¹⁹⁹ In this mechanism, the basic carbonate anion first causes elimination of hydrogen bromide to produce isobutene, whose subsequent protonation affords the electrophile that is responsible for the aromatic substitution. This mechanism explains the necessary presence of sodium carbonate as the base needed to promote the E2 elimination. Furthermore, the 24 hour reaction time and high temperature of 70 °C are

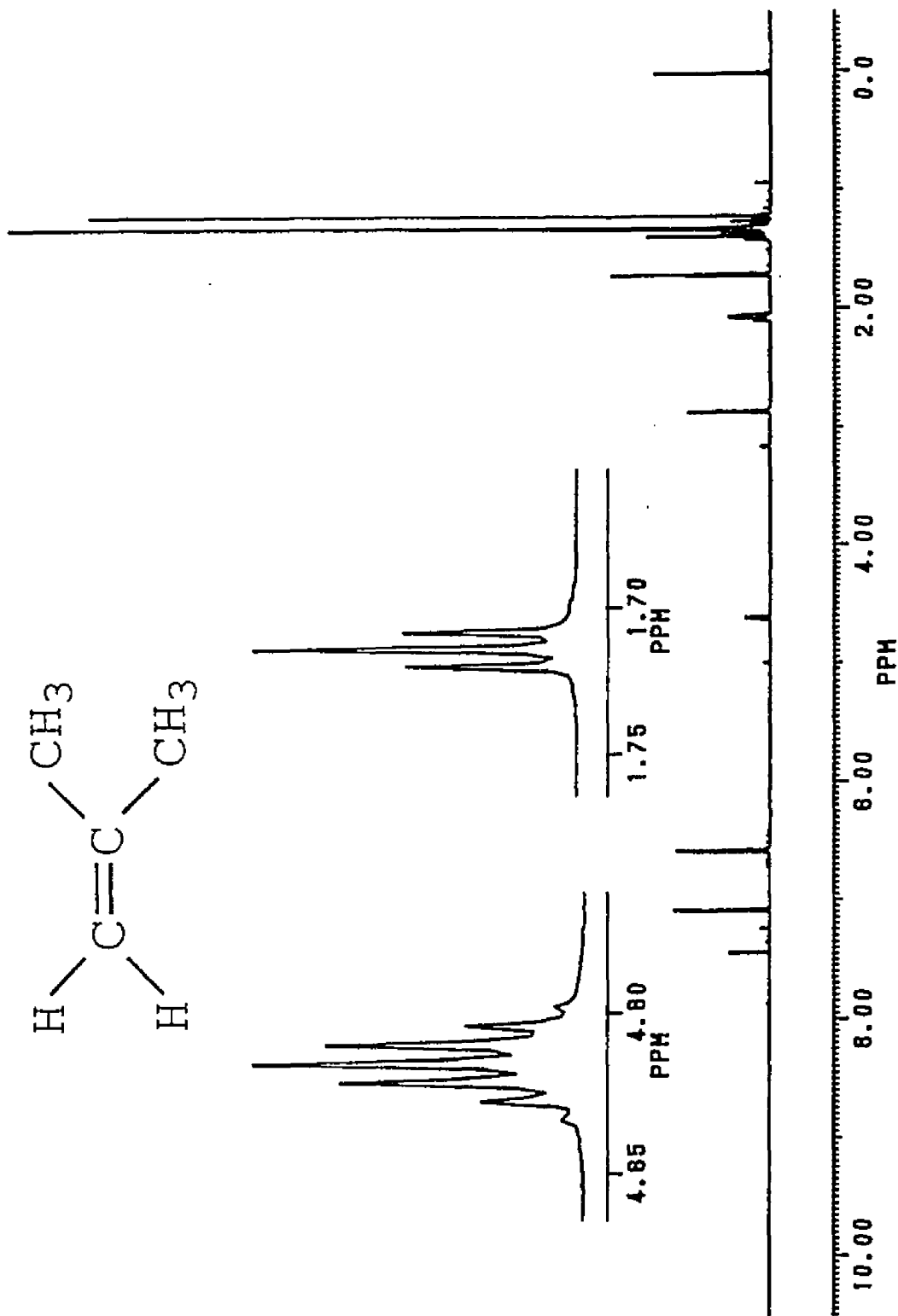


FIGURE 8. ^1H NMR Spectrum Showing Isobutene Formation in the Reaction Mixture.

more consistent with the conditions needed for elimination and are atypical of those normally employed in Friedel-Crafts reactions.^{8,27} It would also explain why tert-butyl chloride, being more difficult to eliminate,²⁰⁰ fails to give alkylation under the present conditions.¹ Normally, Friedel-Crafts alkylations using alkyl halides show the reverse order of reactivity where the chloride is more reactive than the bromide.^{40,44} Attractive as this idea is, it failed to meet the experimental test. It was reasoned that the gaseous isobutene would escape from the hot reaction mixture before the alkylation reaction could occur; however, no difference in product yield was observed between an open and the completely closed reaction systems described in Chapter 2. Thus, isobutene is probably not an intermediate in an elimination-protonation mechanism for the Friedel-Crafts reaction, but is merely formed by unrelated side reactions instead.

One major byproduct that still remains tentatively identified is di-tert-butyl ether. Its ¹H NMR spectrum consists of only a singlet that, besides hydroxyl protons, is the resonance whose chemical shift is most affected by the composition of the reaction mixture. Values of δ 1.17-1.21 were observed in spectra of various reaction mixtures, which is between the δ 1.25-1.26 range reported for di-tert-butyl ether in the literature^{201,202} and the δ 1.12 chemical shift of a 0.19 M solution of tert-butyl methyl ether in

the same solvent system that was employed for the spectrum of the reaction mixture. This volatile compound is the only component of the reaction, other than isobutene, that is removed when the original carbon tetrachloride solution is rotary evaporated under aspirator pressure and the residue redissolved in acetone- d_6 for NMR analysis. A mechanism for the formation of di-*tert*-butyl ether from di-*tert*-butyl carbonate has been proposed by Olah¹⁷² and is likely to apply here. Di-*tert*-butyl carbonate itself is not observed, nor would it be expected to survive the electrophilic conditions of the reaction. The amount of di-*tert*-butyl ether formed in the reaction mixture is variable, being low when quantitative formation of 2,5-di-*tert*-butylhydroquinone is obtained and high when incomplete alkylation occurs. Whether it is present in the reaction mixture as a byproduct of a completely unrelated reaction of *tert*-butyl bromide or is made by the actual intermediate causing the electrophilic aromatic substitution is unclear at this time and deserves further study.

Finally, both silica gel and sodium carbonate are required for complete alkylation to occur. A nearly quantitative yield of 2,5-di-*tert*-butylhydroquinone is obtained if a reagent-grade sample of "anhydrous" sodium carbonate is taken directly from the bottle. Complete drying of the sodium carbonate¹²⁴⁻¹²⁶ at 275 °C in a furnace and the use of procedures that avoid inclusion of

water from any other source effectively stops the Friedel-Crafts alkylation from occurring. Thus, a trace amount of water serves a necessary role as a cocatalyst in a manner similar to other Friedel-Crafts alkylations conducted under more traditional conditions.⁷¹ The function of the sodium carbonate and its trace amount of water in promoting the reaction is uncertain at this time. Nor is it clear what role, if any, is played by absorption of hydroquinone or *tert-butyl* bromide to the surface of silica gel. It is hoped, however, that application of the techniques developed in this research in kinetic and other experiments will contribute to a better understanding of the mechanism of this intriguing reaction.

CHAPTER 4

Educational Implications: Microscale Chemistry

Microscale chemistry, which is characterized by a 100- to 1000-fold decrease, reduces the quantity of starting materials used in chemical reactions from grams to milligrams, characteristically 150 mg or less.²⁰³⁻²⁰⁵ Its development corresponds to an increasing awareness of the environmental, health, and safety issues that chemistry laboratories pose. While unique problems exist with this scale of experimentation, external events, particularly budgetary concerns, have encouraged predictions that most colleges and universities will adopt microscale methods in many, if not most, of their student laboratories.^{205,206}

Public officials are being forced by an increasingly vocal segment of voters²⁰⁷ to adopt a policy of minimal taxation, which has resulted in a reduction of funding to most levels of government including higher education. At the same time, students and parents complain that tuition is increasing too rapidly^{208,209} and wish administrators at institutions of higher education to hold the costs down. Seeking areas to reduce expenditures, administrators might conclude that the student laboratory is not altogether cost effective,^{210,211} and may try to progressively eliminate laboratory experimentation starting with the freshman and

sophomore courses. Experimental seminars,²¹² interactive video computer programs,²¹³ or a combination of the two²¹⁴ are being carefully examined as possible alternatives to chemistry laboratories for undergraduates.

There are several factors that would seem to justify the elimination of lower-division laboratories. One is that some inherent hazards to health and safety are always posed by laboratory equipment and even supposedly benign chemicals,²¹⁵ although student laboratories are generally considered to have a good safety record. Second is the litigious nature of society,²¹⁶ which creates some anxiety in administrators and leads to serious questions concerning the usefulness and effectiveness of student laboratories. Third, the costs of operating student labs^{206,217-220} are increasing while, conversely, most colleges are seeking to reduce expenditures or, at least, to control their growth. In the above context, the student laboratory is both highly visible and very expensive. The final, and most damaging, aspect is that some researchers in education have not been able to specifically identify cognitive benefits for the student having a traditional laboratory experience.^{210,221} The results of Smith, Jones, and Waugh²¹³ suggests that use of interactive videodisc laboratory simulators have given students a better grasp of basic theory of phenomenon than does performing the actual experiment.

The laboratory has not always been a routine part of chemistry courses in the United States. Introduction of laboratories at the college level was started in the late 1800s by American chemists who had studied abroad to gain laboratory experience.^{61,62,222} Since then, laboratories have become an integral part of virtually all undergraduate chemistry courses. It seems heretical to suggest their elimination, but this is under discussion in the academic community^{206,220,221,223} notwithstanding recent calls from the American Chemical Society for an increase in laboratory usage.²²⁴

Microscale organic chemistry is not a new concept to research scientists, but has a history that spans more than a century²²⁵ and was the basis of the semimicro laboratory techniques used in the mostly discontinued qualitative analysis course.²²⁶ Microscale laboratory manuals are increasingly available for the various levels of chemistry students, but the greatest effect has been in organic chemistry.²²⁷⁻²³⁶ In the next ten years, most collegiate organic laboratories are predicted to convert to microscale experiments.^{205,206} Implementation has occurred despite problems which are unique to or greatly exacerbated by microscale. Microscale experimenters must exercise more caution because errors incurred in the manipulation and/or contamination of small samples are more significant to the final results than when using macroscale. For example,

distillation procedures are difficult because the ratio of wetted glass surface area to the volume of the distillate increases as the size of the sample is reduced. The same is true for the ratio of the surface area of a sample to its volume, which is important in the case of air-sensitive compounds. The greater attention to detail does, however, have learning benefits for the students and, in addition, decreases breakage of expensive glassware and minimizes spills of potentially hazardous chemicals.²¹⁷

When a new physical scale of experimentation evolves, there may be little or no specialized glassware to conduct experiments efficiently. The efforts of two independent developers of microscale experiments, one group centered around Dana W. Mayo of Bowdoin College and the other around Kenneth L. Williamson of Mount Holyoke College, led to the introduction of two distinct glassware kits. These kits represent differing philosophical orientations. The Mayo, Pike, and Butcher^{227,229} implementation, which most other authors of organic laboratory manuals now emulate,²³¹⁻²³⁶ is essentially a miniaturization of standard glassware and was designed by Ace Glass, Inc.²³⁷ and are used in a series of experiments which often require other instrumentation to verify results. The Ace kit is shown in Figure 9. The simpler microscale laboratory kit manufactured by Kontes²³⁸ for Williamson's more novel and less expensive approach to experimentation is shown in Figure 10, where it is compared

with the threaded research microscale kit of Kontes that was employed for certain experiments described in Chapters 2 and 3. The microscale glassware used in Williamson's texts^{228,230} is unique in the field, and stems from the tradition of innovative and inexpensive laboratory setups of Louis Fieser,²³⁹ whose macroscale laboratory manual was adapted to microscale by Williamson.

Appropriate techniques,²⁴⁰⁻²⁵³ reactions,²⁵⁴⁻²⁸⁵ and equipment²⁸⁶⁻²⁹⁴ have to be invented, rediscovered, or adapted to cope with problems that microscale experiments create. Communication of these innovations to the *Journal of Chemical Education* has occurred with such regularity that now there is a continuing section devoted entirely to microscale news. These communications also include tested suggestions about the use of instrumentation²⁹⁵⁻²⁹⁹ and miscellaneous helpful hints³⁰⁰⁻³⁰⁵ about problems that are encountered in microscale experimentation. To cite but one example, controlled heating at a specified temperature is a technical problem that requires a better solution. Most editions of microscale organic lab manuals²²⁷⁻²³⁶ recommend a sand bath, made by placing sand in a heating mantle, as the heat source, but this has not been satisfactory because slow and uneven heating usually occurs and can cause the solvents to flash. Experimentation shows that mounting an aluminum heat sink on a hot plate provides a more uniform and controlled heating for most microscale experiments.²⁸⁶

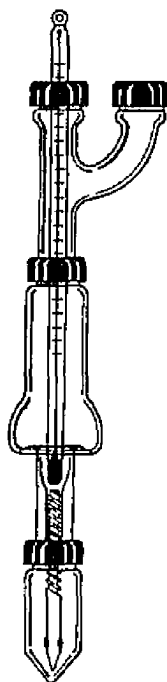
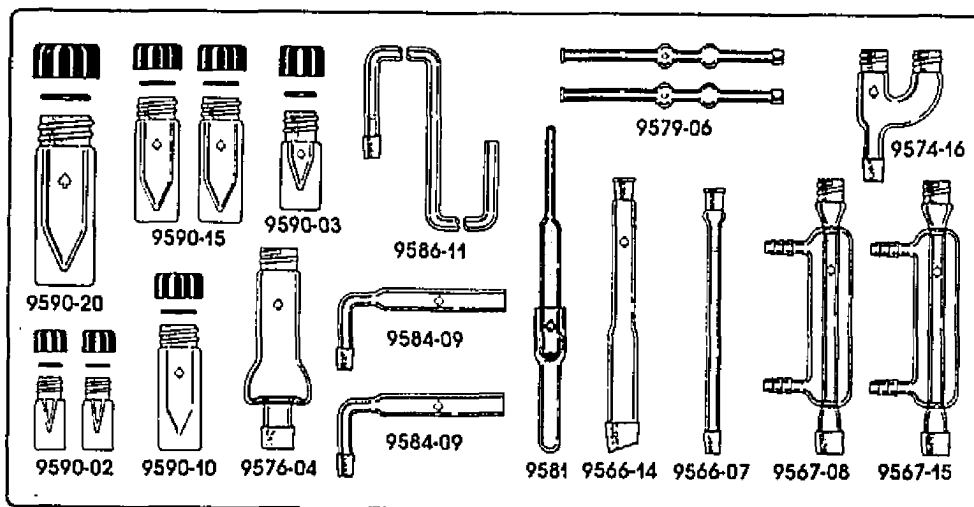
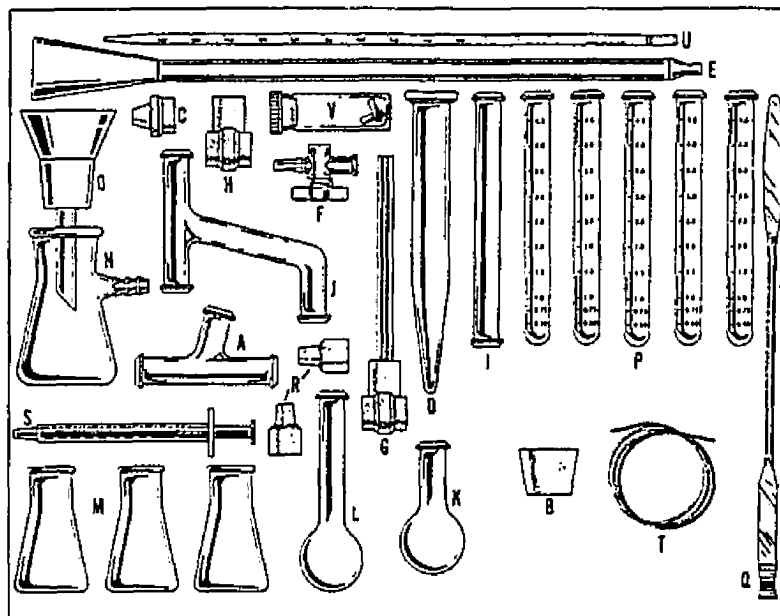


Figure 9. The Original Deluxe Micro/Mini-Lab Glassware Kit of Ace Glass, Inc. A Setup Employing the Spinning Hickman-Hinkel Distillation Column Is Also Shown. Reproduced with Permission.

Improved Standard Kit



The Research Kit

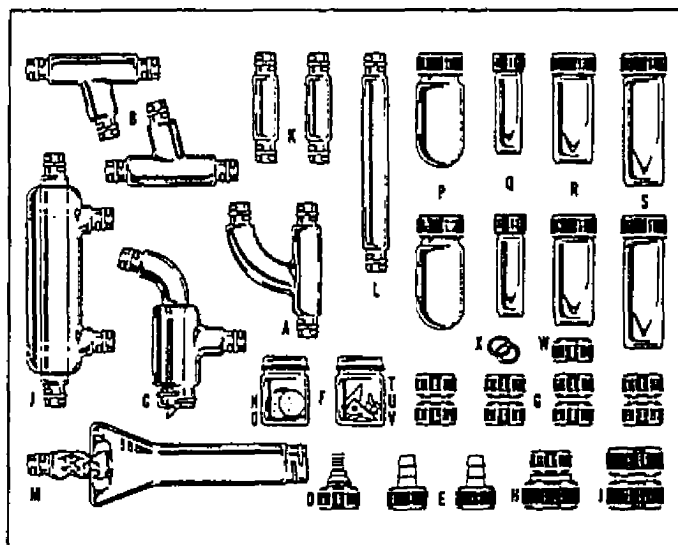


Figure 10. The Improved Standard Williamson and Threaded Research Microscale Glassware Kits of Kontes. Reproduced with Permission.

Commercial models are now available, but some departments make their own.²¹⁹ Even in the face of these problems, laboratories are being increasingly converted to microscale with unusual rapidity considering the historic conservatism of most educational institutions. An important factor in this rapid adoption of microscale organic chemistry is the laboratory guidelines set forth by the Occupational Safety and Health Administration's²¹⁵ (OSHA) Laboratory Standard 29 CFR Part 1910.1450.

The original impetus to investigate microscale organic experiments was the health and safety concerns about air quality for students exposed to low-level concentrations of common solvents.³⁰⁶⁻³¹² The earlier guidelines set forth by OSHA were for industrial laboratories, but these were later extended to include academic laboratories. Even stricter guidelines for compliance are now being considered by Congress.³¹³ To attain these goals, laboratories would have to be better ventilated; however, purchasing new hoods would be too costly in view of fiscal constraints discussed earlier. These concerns, coupled with greater awareness by students of the health hazards caused by exposure to common reagents, might have caused the elimination of the student organic laboratories completely.

Microscale organic experimentation changes all this by radically decreasing the amounts of reagents that students work with and, consequently, the amount of chemicals in the

gaseous state. Wood²¹⁷ states that microscale organic experiments can now be conducted safely in any room. Other safety factors are noted^{206,220} such as: reduced risk from fires and explosions, reduced risk of cuts because of less breakage of glassware, and reduced risk of spills because students work more carefully with these smaller components. Additional benefits^{217,314} may appear with reduction of the experimental scale because of increased safety in chemical stockrooms by limiting the amounts of chemicals needing storage. Thus, improper storage of chemicals and overall clutter is minimized. It is a happy coincidence that doing the right thing, microscale, for the right reason, safety, is also less expensive. Ironically, the major inducements cited by advocates of microscale organic chemistry are primarily economic.

Economy derived from this scale occurs in many ways. When the provisions of CFR 29 1910.1450 went into effect and set permissible exposure limits to hazardous chemicals for employees in all laboratories, estimations were that post-secondary institutions would spend nearly \$4 million annually to comply with regulations, including about \$1.7 million spent on hood monitoring and maintenance.²¹⁵ This does not include replacement of presently inadequate hoods nor addition of new hood space to handle potential dangers to employees. Since microscale increases the quality of the air by reducing the amounts of reagents in use, there

is usually little need for expensive retrofits of hoods in most laboratories. If additional and more powerful hoods had been needed, there would have been increased demand on heating and cooling systems. Therefore, being able to keep the existing hoods also represents a savings of energy.²²⁰ One college estimated that \$250,000 was needed for a hood retrofit, but it spent only \$25,000 to implement microscale organic labs.³¹⁵

Second, there is a decrease in the cost of chemicals used in microscale labs. It is axiomatic that using lesser quantities will cost less; however, there is another facet to this economy since the total cost must now include its disposal.^{206,217,218,220} Large containers, even if they contain only a gram of chemical, cost more to dispose of than small containers. Large containers often require expensive transfer equipment to avoid the twin hazards of exposure and contamination, and also require larger and more specialized storerooms. Wood²¹⁷ has estimated that large chemical containers may be 50% more costly than small containers regardless of the scale of the experiments.

Third, there is a significant reduction in hazardous waste and the attendant cost of its disposal when using microscale. In a study by Chloupek-McGough,³¹⁶ the annual production of liquid waste fell from seven gallons to one, and solid waste fell from three gallons to one. Zipp²¹⁸ reported similar waste reduction. Disposal of hazardous

chemical waste has become expensive, and it is becoming very difficult to find sites that are willing to accept the waste.³¹⁶ Further savings could be achieved by recycling hazardous waste materials, and microscale quantities makes recycling especially feasible.²⁰⁶ Potential expenses do not end with payment for proper disposal. Institutions are also liable for future contamination caused by their waste.²¹⁵ Thus, there is an extreme interest in reducing the amount of hazardous waste to an absolute minimum.

A fourth potential savings is realized due to less breakage of glassware because of greater student care and thicker walled containers.^{206,217,218,220} Mayo estimated that Bowdoin College has decreased by 75% the expenditures on chemicals consumed and equipment breakage since the introduction of microscale organic laboratories.³¹⁵

Not all savings due to microscale laboratories are monetary. Pickering³¹⁷ demonstrated in a study of time efficiency that students finished experiments approximately 33% faster when microscale techniques were employed. This allows the instructor to assign more experiments, require more thorough characterization of products, or utilize the time to include more theoretical aspects of the experiment through increased laboratory discussions, which has the desirable outcome of increasing, in effect, a three hour laboratory to four hours with no additional demand on the laboratory facilities or the student's time.

A final saving may occur in insurance and litigation. Since microscale is a new concept, there is insufficient data to estimate how insurance and litigation costs will change, but there should be significant savings. It is reasonable to project less litigation due to more limited exposure to hazardous chemicals and fewer accidents. For example, Pike²⁰⁶ states there were no reports of fires or explosions during the first six years of his experience with microscale organic laboratories.

Microscale labs may have only postponed the debate on the fate of the undergraduate laboratory tradition, but eventually the disproportionate expense of maintaining these laboratories may cause their demise. For example, the budget of the Department of Chemistry and Physics at Middle Tennessee State University for the fiscal year 1991-1992 was \$170,141 for supplies and equipment, of which more than 75% was spent on undergraduate laboratories.³¹⁸ If the costs of lower-division laboratories could be reduced, academic scientists could use the savings to support their research or enhance the undergraduate curriculum. Federal funding from grants to higher education may even be reduced during the government's attempt to control the deficit,³¹⁹ and institutions may have to resort to novel approaches to surmount the fiscal problems they face.

Considering these problems, Toothacker²¹¹ proposes a solution that merits careful consideration. It consists of

offering a laboratory course called Experimentation at the end of the sophomore year, which provides science majors an opportunity to learn and develop the laboratory techniques and mathematical skills associated with data acquisition and analysis. This course would have as its goal a genuine empirical exploration where students define a scientific question, propose an experiment, assemble the equipment, collect and analyze the data, interpret their findings, and report the results in some acceptable format. After this course, student laboratories would be incorporated into upper-division courses and would be more focused on current scientific problems.

Whatever words are used in future debates on student laboratories, the underlying issue is economics. Whether microscale experimentation can reduce costs to a level that the student laboratory tradition can continue or not is not yet clear. The answer may be the affirmative in the short term, but the more distant future should probably be viewed with increasing pessimism.

CHAPTER 5
Conclusions

The literature of Friedel-Crafts alkylation chemistry and heterogeneous catalysis, especially that of silica gel, is reviewed in the introductory chapter. Silica gel can be employed in organic synthesis as a solid support for many inorganic reagents to accomplish heterogeneous reactions. The weak acidity of silica gel also allows its use alone as a mild and, therefore, a selective acidic catalyst. The heterogeneous nature of such reactions simplifies product isolation, which consists only of filtering the catalyst and evaporating the solvent. These properties of silica gel were exploited by Masaru Hojo,^{1,73} who found that a 92% yield of unusually pure 2,5-di-*tert*-butylhydroquinone can be isolated when a carbon tetrachloride solution of hydroquinone and *tert*-butyl bromide is stirred in contact with silica gel (Wakogel C-300) and finely powdered sodium carbonate at 70 °C for 24 hours. This reaction was studied as part of the doctoral research being reported here.

Only a slight increase in yield was obtained when the temperature was increased from 70 to 80 °C; however, the alkylation was incomplete at 60 °C. Therefore, the optimum reaction temperature is near 70 °C. Hojo's claim that the presence of sodium carbonate is necessary to obtain high

yield was confirmed, as was the necessity that silica gel also be present. Although the silica gel must be dried for five hours at 170 °C in a vacuum oven (4 mmHg) if the reaction is to be successful, drying the sodium carbonate in a box furnace (275 °C overnight) effectively stops the Friedel-Crafts alkylation. Hence, a trace amount of water must serve a necessary role as a cocatalyst. Isobutene and its olefinic dimers are formed in small amounts from *tert*-butyl bromide during the reaction; however, isobutene is not regarded as a source of the electrophilic intermediate in the Friedel-Crafts *tert*-butylation because the extent of alkylation obtained in a closed reaction vessel is the same as when the stirred and heated reaction was conducted in an open system whose thermostated reflux condenser was kept at a temperature above the boiling point of isobutene.

A proton NMR method of multicomponent, trace-organic analysis was developed to identify the numerous, minor byproducts and also to quantify the product distribution. It is expected that application of this analytical method in kinetic and other experiments will contribute towards a better understanding of the function of silica gel in the mechanism of the reaction. Although the reaction mixture has a somewhat complicated NMR spectrum with many peaks in the aromatic, olefinic, hydroxyl, and alkyl regions, the spectra of all components of the product distribution were discernible, and most of these have now been identified by

comparison with the spectra of sixteen reference compounds. Furthermore, NMR spectroscopy proved a powerful analytical technique to establish the relative concentrations of all species present in the reaction mixture because the vast majority of their individual resonances were sufficiently resolved to permit accurate integration. An important exception to this was aromatic protons of the starting hydroquinone and its 2,5-di-*tert*-butylated product, which required the addition of trifluoroacetic acid before an acceptable resolution of their singlets was obtained. Finally, it was discovered that storing acetone- d_6 , whose 30% solution in CCl_4 was employed as the NMR solvent, over 4A molecular sieve causes the formation of D_2O and aldol condensation products. This contamination affected the chemical shift of the solutes and also the integration of their exchangeable protons in early spectra, which had to be repeated using undried solvent.

Since the Doctor of Arts is fundamentally a college teaching degree, an extra chapter entitled "Educational Implications" provides a detailed review of the microscale literature, including over 50 citations from the *Journal of Chemical Education* pertaining exclusively to microscale organic experiments. Other articles extol the substantial economic and pedagogical advantages found in the conversion of laboratories to microscale, where amounts rarely exceed 150 mg. The preexisting trend of using smaller quantities

of reagents was accelerated by the leadership of Kenneth Williamson and the group of Mayo, Pike, and Butcher. The greater environmental awareness of students, the expense of operation, and the force of law brought by inclusion under OSHA's regulations have caused concerned academic chemists to seek alternatives to standard laboratory practices and have raised doubts as to the viability of undergraduate laboratories. Microscale experimentation may have diverted the conversation from more radical solutions, but the ultimate fate of lower-division laboratories in chemistry is not yet certain.

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