THE SYNTHESIS OF

QUINONE-CAPPED CYCLODEXTRINS

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Michael Cossette

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This thesis is submitted in partial fulfillment of the requirements for the degree of

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Michael Cossette

Author

Approved, February 1988

Christopher J. Abelt

Christopher J. Abelt

Randolph A Coleman

Randolph A. Coleman

Trevor B. Hill

Trevor B. Hill

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ABSTRACT

The disulfonic and dicarborboxylic acid chlorides of 1,4-benzoquinone, 1,4-naphthoquinone, and 9,10-anthraquinone were investigated as possible capping agents for β-cyclodextrin.

Attempts to synthesize benzoquinone-2,5-dicarboxylic acid chloride, as well as its 3,6- dichloro derivative, failed when approached through the intermediate 1,4-dicarbomethoxy-cyclohexa-1,4-diene-2,5-diol. In an effort to remove possible complications owing to the beta-keto position of the dicarboxylic acid derivatives, benzoquinone-2,5-diacetic acid chloride was successfully synthesized; however, attempted reaction with β-cyclodextrin failed, presumably from side reactions involving alpha proton reactivity in the solvent pyridine.

Synthesis of both the 2,6- and 2,7- dicarboxylic acid chlorides of anthraquinone was accomplished; reaction with β-cyclodextrin led to approximate yields of 15-18% of modified cyclodextrin. The large intramolecular reactive center distance and rigid planarity of this capping agent should enforce regiospecific A,D capping, thereby ruling out dicapping as a competitive mechanism, and sidestepping some of the more difficult problems in work-up and spectral interpretation.

After isolation and purification of the bulk product, a monocap derivative was supported by TLC, IR, UV and proton NMR. A definite confirmation of structure was not possible with available carbon-13 NMR.

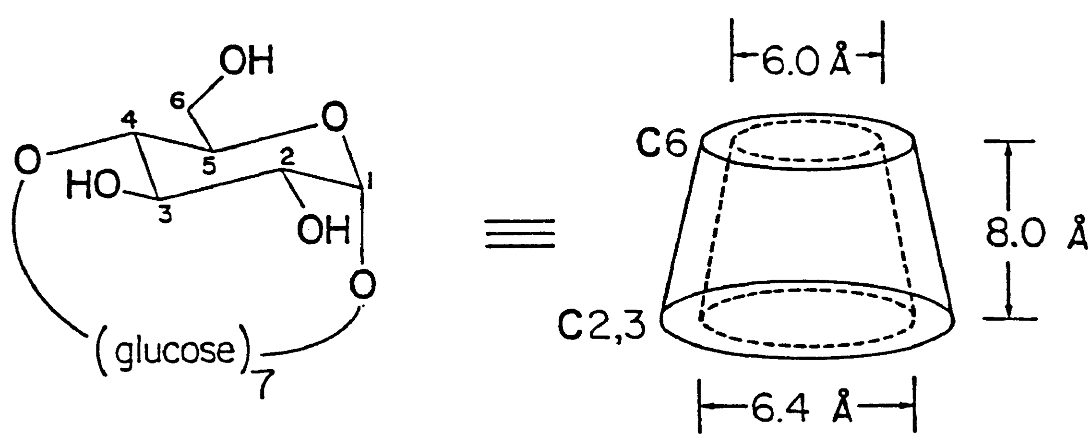
THE SYNTHESIS OF

QUINONE-CAPPED CYCLODEXTRINS

INTRODUCTION

For the long-range direction guiding this project, the physical and chemical properties of two well-known classes of compounds, the p-quinones and the β-cyclodextrins, will be used to create a novel macromolecular system with potential to serve as a photoinduced electron transfer catalyst having a specific micro-environment. The viability of this goal, as well as the photophysical properties of the quinones, are analyzed in **PRELIMINARY PHOTOPHYSICS.** The organizing environment is provided by β-cyclodextrin, a cyclic heptamer of glucose with a toroidal shape which defines an ether-like cavity lined by rings of C_3-H atoms, glucosidic oxygens, and C_5-H atoms.

Figure 1. Organizing Host: β-cyclodextrin.

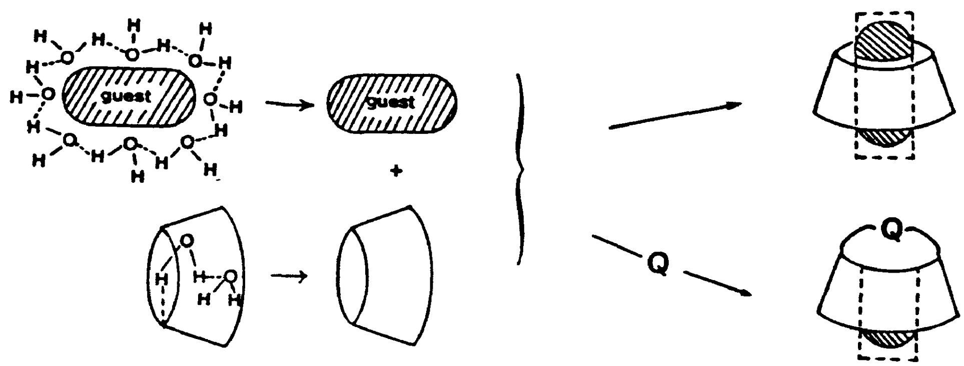


The relatively rigid secondary C_2-OH and C_3-OH groups are located at the slightly more open face, while the primary C_6-OH groups are located on the opposite rim, and can rotate to partially block the cavity.

The ether-like nature of the cyclodextrin cavity can be observed experimentally: when an aqueous cyclodextrin solution is treated with p-tert-butylphenol, the resulting UV spectrum is identical with the absorption of the phenol in dioxane, yet very different from readings obtained in aqueous amylose.[1] When an aromatic molecule in an aqueous system prefers the internal environment of the macromolecular cyclodextrin, it has been postulated that a hydrophobic interaction provides the driving force for the host-guest binding.[2] This interaction overcomes the hydrophobic destabilization originating in the entropically unfavorable orientation of water molecules on both the surface of the hydrophobic guest dissolved in water, and the interior of the cyclodextrin cavity.

This theory implies that a decrease in the hydrophobic surface area exposed to water would lead to a favorable hydrophobic interaction. From this perspective, Figure 2 shows how capping a cyclodextrin host should cause significantly increased hydrophobic binding of a guest.[3] An increase in the binding constant for included moieties in rigidly-capped cyclodextrins has been measured for a number of appropriately-sized guests.[4] A quinone-capped cyclodextrin will not only have this binding pocket, but also a catalytic electron-accepting species in close proximity to any guest.

Figure 2. Thermodynamics of Host-Guest Binding



Cyclodextrins have already been found to influence a variety of chemical reactions,[5] mainly owing to the restricting and organizing environment provided by the cavity. The specific effects vary. Cyclodextrin has altered the photochemistry of bound guests by: enforcing specific conformations on a molecule undergoing conformationally dependent photoreactions,[6] restricting the space available for molecular motions in unimolecular reactions,[7] and exerting regiochemical influence over the fission products of bimolecular reactions.[8] In the present study, guests will be chosen which maximize the possible effects on product stereochemistry, identity, and distribution.

The success of the proposed catalytic study will hinge on the viability of synthetic pathways to quinone-capped cyclodextrins; it is the immediate goal of this project to investigate those pathways.

PRELIMINARY PHOTOPHYSICS

(A) THEORETICAL

The viability of the capped cyclodextrin as a photoinduced electron transfer catalyst can only be established after its synthesis; however, a preliminary consideration of the photophysical parameters of the proposed complex should allow us to rationalize the time and effort involved in a synthetic survey of possible target molecules.

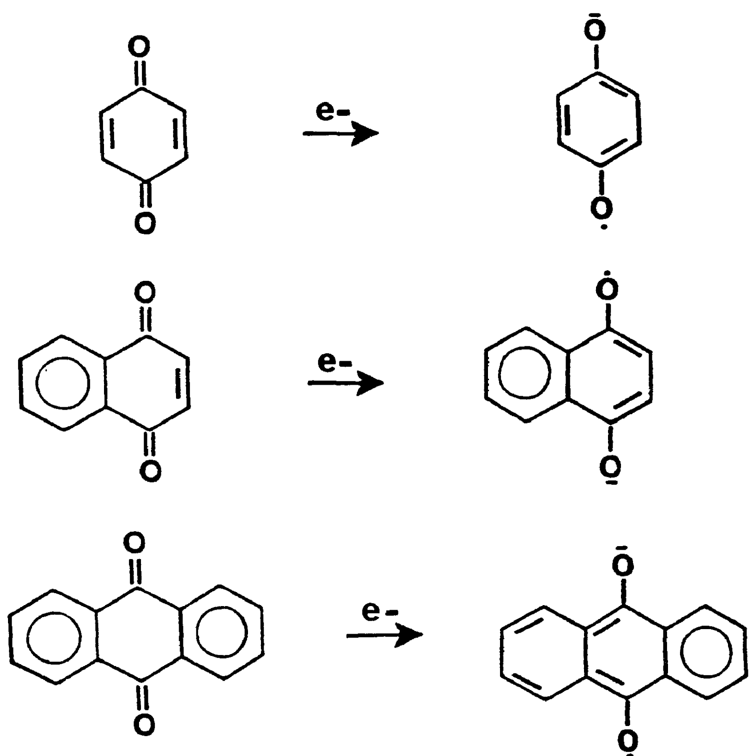
The p-quinones owe their photochemical usefulness to the cross-conjugated dienone structure, which can accomodate an extra electron as a radical anion, stabilized to varying degrees by the aromaticity imparted from the resulting resonance structures.(Figure 3) These valence-bond representations emphasize localized aspects of electron distribution, and are of some importance when considering the stability of the radical anion in an aqueous system. Benzoquinone has more to gain from its transformation in (i) than naphthoquinone in (ii), or anthraquinone in (iii); the latter two structures are already stabilized by benzenoid rings. Additionally, the concentration of the charge on the carbonyl oxygen in (i) should be greater than in (iii), if the increasing conjugation implies, from a molecular orbital viewpoint, delocalization of electron density.

Figure 3. Radical Anions of p-Quinones

(i) Benzoquinone

(ii) Naphthoquinone

(iii) Anthraquinone

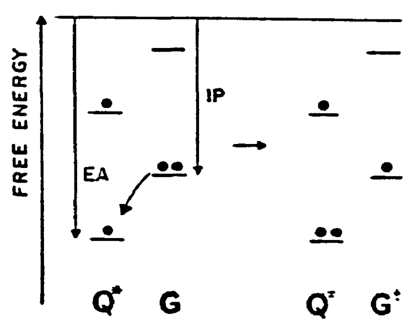


Can these effects be observed empirically? Benzoquinone in water can be reduced to hydroquinone by UV irradiation,[9] and (i) has been postulated to be involved in an initial hydroxylic hydrogen abstraction which would be energetically unfavorable prior to the generation of the radical anion.[10] In contrast, the irradiation of anthraquinone in water by visible light gives a mixture of various hydroxy-anthraquinones, rationalized by a mechanism involving triplet abstraction of an electron from aqueous hydroxyl anion.[11] In this last process, one notes the characteristic absence of hydroquinone products, which in the present study would inactivate the cap to electron transfer from an included guest. If aqueous interaction by irradiated quinones is competitive with electron abstraction from cyclodextrin guests, these observations suggest that anthraquinone caps would be more reliable than benzoquinone caps.

The energetics of the electron transfer can be depicted by a simplified molecular orbital representation:[12]

Figure 4. <u>Energetics of Electron Transfer(I)</u>

(Sensitizer as Electron Acceptor)



IP = Ionization Potential

EA = Electron Affinity

Q = Quinone

G = Guest

For the goals of the present study, the electronically excited states of the quinones are the electron acceptors, with reduction potentials which are greater than the ground state oxidation potentials of the donor guest. With quinonoid planar aromatics(**Q**), the geometry of the excited state does not differ significantly from the ground state; if we momentarily assume that the entropy changes associated with the formation of the radical ion pair is negligible in the capped cyclodextrin(**CD**) complex, then the free energy of excited state quenching by electron transfer(G_{et}) from an included guest(**G**) can be calculated from the Weller equation:[13]

Equation 1. $$G_{et} = -E(Q/Q^{\cdot -}) + E(G^{\cdot +}/G) - e^2/cd$$

Choosing guest molecules with oxidation potentials that are less than the excited state reduction potential of the quinones, approximately 1.8V,[14] enforces favorable thermodynamics for electron transfer. This does not, however, suggest that the rate of electron transfer will be unaltered. To address this, we must first define the quantum yield for electron transfer quenching:[15]

Equation 2. $$\Phi_{et} = \phi_{es} \frac{k_q[A]}{k_q[A] + k_d + k_{q'}[A]}$$

where ϕ_{es} is the efficiency of excited state formation, k_q is the bimolecular rate constant of electron transfer, and k_d the unimolecular rate constant for excited state decay. Competitive bimolecular quenching reactions, such as the previously mentioned photoreduction in water, are contained in the term $k_{q'}$. We can approach fuller rate expressions by writing out the possibilities open to the complex upon excitation:[16] (Equation 3)

$$\begin{array}{ccccccc}
G(CD) + Q^{*} & \underset{k_{-diff}}{\overset{k_{diff}}{\rightleftharpoons}} & G(CD)\ Q^{*} & \underset{k_{-a}}{\overset{k_{a}}{\rightleftharpoons}} & G^{\overset{+}{\cdot}}(CD) + Q^{\overset{-}{\cdot}} & \underset{k_{-p}}{\overset{k_{p}}{\rightleftharpoons}} & G^{\overset{+}{\cdot}} + (CD) + Q^{\overset{-}{\cdot}} \\
\downarrow k_{d} & & & & \downarrow k_{r} & & \\
G(CD) + Q & & & & G(CD) + Q & &
\end{array}$$

where $\mathbf{k_{diff}}$ and $\mathbf{k_{-diff}}$ are the diffusion-controlled rate constants, $\mathbf{k_a}$ and $\mathbf{k_{-a}}$ are the bimolecular activation energy controlled rate constants for electron transfer, $\mathbf{k_r}$ is the rate constant for electron transfer to ground state, and $\mathbf{k_p}$ the rate constant for the dissociation of the radical ions.

Applying the steady state approximation to these equations, assuming that electron transfer is exothermic, and that $\mathbf{k_{diff}}=\mathbf{k_{-diff}}$, leads to the expression:[17]

Equation 4. $$\frac{1}{k_q} = \frac{1}{k_a} + \frac{1}{k_{diff}}$$

From this derivation we can draw two conclusions: first, when electron transfer is slow ($\mathbf{k_a} \ll \mathbf{k_{diff}}$), the measured rate is related to the activation energy barrier for electron transfer; second, when electron transfer is rapid ($\mathbf{k_a} \gg \mathbf{k_{diff}}$) the observed rate is simply the diffusion-controlled rate constant for the medium in which the reaction takes place. We can relate $\mathbf{k_a}$ to the electronic and nuclear barriers to the rate of electron transfer:[12]

Equation 5. $$k_a = A[k_{et}] = A[k \exp(-G\#/RT)]$$

where **k** reflects the electronic barrier of the reaction, and **G#** is the free energy of activation reflecting nuclear barriers. The quantity **A** represents the collision frequency at unit molar concentration of reactants within the encounter complex.

How do Equations 1-5 allow us to make some tentative judgement on the theoretical feasibility of electron transfer from a cyclodextrin guest molecule to an electronically excited quinone cap in an aqueous solvent system? In such a system, we could expect that the rate of electron transfer, relative to solution, would be reduced. The magnitude of $\mathbf{k_{et}}$ depends on the ability of the quinone and guest to freely interact through various electronic and nuclear configurations until finding an arrangement that permits electron transfer to occur. In the cyclodextrin complex, the geometry of the encounter is determined by the cavity size and shape; although the species are held in close proximity, the distance of closest encounter is smaller.

This critical point can be quantified by redefining the electronic barrier of the reaction:[18]

Equation 6. $$k = k_o \exp[-\beta(d-d_o)]$$

where k_o is the maximum probability of passage of an electron at the intersection point, d_o the electronic contact distance, and $d-d_o$ the electronic edge to edge distance, which is inversely proportional to the amount of electron overlap. The rate of electron transfer, which decreases with separation distance, can be calculated from values of β, which usually range from 0.9-2.0Å^{-1}.

Two qualities of the parameter β allow this theoretical treatment of electron transfer to be useful: it is not reflective of the relative orientation of donor and acceptor, nor of the nature of the medium through which the electron travels. The first aspect helps us interpret the possible spatial orientations open to donor and acceptor orbitals. A symmetrically capped cyclodextrin could theoretically have its quinone orbitals situated orthogonal to those of an included aromatic; however, the flexibility of the cyclodextrin and the slight, but definite rotational ability of a quinone cap help guarantee that if orbital overlap exists, it will be electronically meaningful. From a rigorous theoretical standpoint, there is always some residual overlap between poorly overlapping wave functions and the orbitals they describe. The dimensions of the cyclodextrin guarantee that the quinone and included guest will be separated by less than 7Å, and applying Equation 6 ensures k_{et} on a reasonable order of magnitude of $10^9 s^{-1}$.

The independence of β on the medium through which the electron travels does not completely resolve the question of how differing micro-environments within the cyclodextrin complex will effect processes after electronic excitation. The final term in Equation 1 takes into account the coulombic interactions and solvent stabilization effects on the species formed after electron transfer. Since the transition state has charge-like character, solvent polarity should effect the quenching of excited states by electron transfer. The cyclodextrin, however, has two distinct environments: an ether-like interior cavity, and an outer region of high polarity. Normally we would expect a polar solvent to separate radical ion pairs into solvated ions; however, separating the cyclodextrin radical ions requires overcoming the electrostatic forces of attraction and creating an entropically unfavorable hydrophobic void in the cavity. The radical cation may also be stabilized by the interior ring of glucosidic oxygens, in a manner analogous to the interaction of crown ethers and inorganic ions. These considerations suggest that developments with the radical cation should be significantly influenced by the organizing capability provided by the cyclodextrin.

Given the feasibility of an initial electron transfer, the host-guest relationship should assist the radical ion pair in avoiding some of the undesirable side reactions associated with electron transfer induced processes. The restricted approach of the radical ion pair should eliminate the chemical reaction of the radical cation with the radical anion to form unwanted products. In the quinone-capped cyclodextrins, reverse electron transfer in aqueous systems should be inhibited by the hydrogen bonding stabilization of the radical anions (i)-(iii) in Figure 3. The semiquinone oxygen atoms are weak bases,[19] suggesting proton association that would severely limit back-transfer of electrons in an aqueous system.

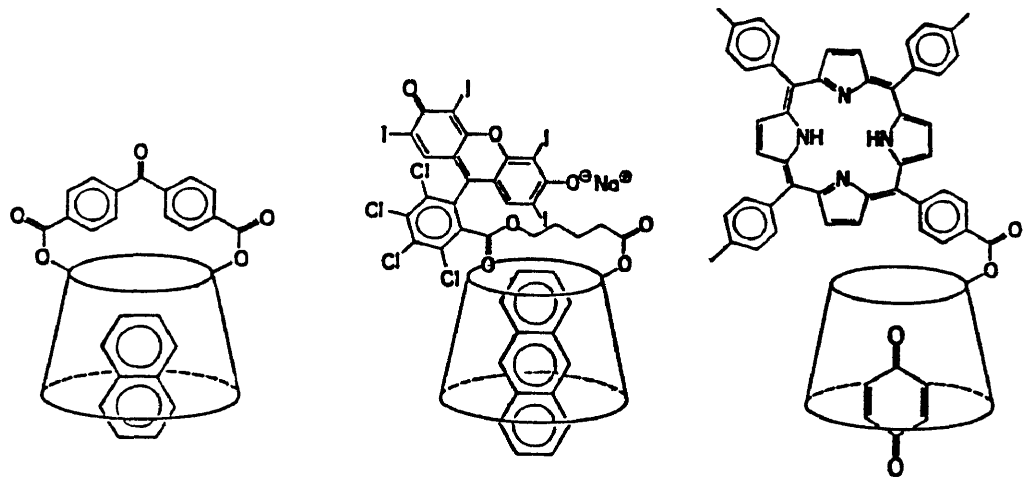
What conclusion can be drawn from this analysis? The most we can claim is that there is no obvious reason, from theoretical considerations, to believe that electron transfer will not occur under the outlined conditions. The fate of the radical ion pair after quenching occurs is less clear, and the demonstration of the effect of the micro-environment supplied by the cyclodextrin is part of the longer range objective, not in the defined scope of this synthetic survey.

(B) EXPERIMENTAL

Given the limitations of theory, a direct appeal to the literature concerning the use of modified cyclodextrin as a photocatalytic system may be more informative. Although there are no available reports of anyone synthesizing a quinone-capped cyclodextrin, three types of modified cyclodextrin have been used as photosensitizers.(Figure 5)

Figure 5. Cyclodextrin Sensitizers

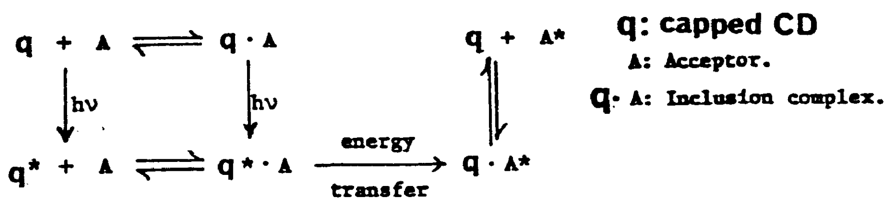
(a)Triplet (b)Singlet Oxygen (c)Electron Transfer



Tabushi and coworkers[20] used cyclodextrin, which was rigidly capped with benzophenone, to investigate specific host-guest energy transfer from triplet cap to included naphthalene derivatives.(Figure 5a) Quenching by this inclusion-energy transfer combination is schematically depicted in Figure 6, and can be compared and contrasted with Equation 3.

Rose bengal, a singlet oxygen photosensitizer, has been singly linked to cyclodextrin, with subsequent observation of enhanced quenching of singlet oxygen by included anthracenes.[21](Figure 5b) Here we see the effect of attaching the rose bengal to the primary face: singlet oxygen formed next to the tethered cap is in close proximity to the included guest, resulting in enhanced quenching.

Figure 6. Quenching by Inclusion-Energy Transfer



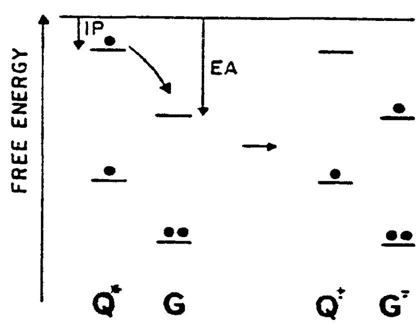
Studies involving electron transfer have involved appending a porphyrin to the primary face of cyclodextrin.(Figure 5c) Here the sensitizer is the electron donor, and excitation of the porphyrin chromophore results in electron transfer to an included quinone. The energetics of the transfer are shown in Figure 7, and can be compared and contrasted with Figure 4.

In one study, 5-(p-carboxyphenyl)-10,15,20-(tri-p-methylphenyl) porphyrin was used as the electron donor, with p-benzoquinone as the electron acceptor;[22] the evidence for photoinduced electron transfer was used to study the effect of the reduction potential of the acceptor on the efficiency of the transfer process. Large acceptors such as naphthoquinone, which may not fit into the cavity as well as benzoquinone, have sufficiently positive reduction potentials to enforce electron transfer;

therefore, the absence of significant e.s.r. activity in a complex of the former, when contrasted with the latter, helps support their hypothesis of inclusion complexation augmenting electron transfer.

Figure 7. Energetics of Electron Transfer(II)

(Sensitizer as Electron Donor)



IP = Ionization Potential

EA = Electron Affinity

In another study,[23] the neutral zinc(II)meso-tetrakis[1-(3-sulfonatopropyl)-4-pyridino]porphyrin was used as the electron donor, with anthraquinone-2-sulfonate as the electron acceptor. These two species normally form a ground state complex; however, in the presence of cyclodextrin, selective association of the quinone to the hydrophobic cavity enforces a separation of the complex, allowing diffusional quenching of the excited donor as it decays to the triplet state.

Although nothing more than suggestive, these studies do indicate that the micro-environment of the cyclodextrin is amenable to photoprocesses such as electron transfer. Additionally, the absence of any theoretical reason to dismiss the viability of the quinone-capped cyclodextrin as a potential photoinduced electron transfer catalyst supports a reasonable commitment to the proposed synthetic survey.

SYNTHETIC STRATEGY

(A) BACKGROUND

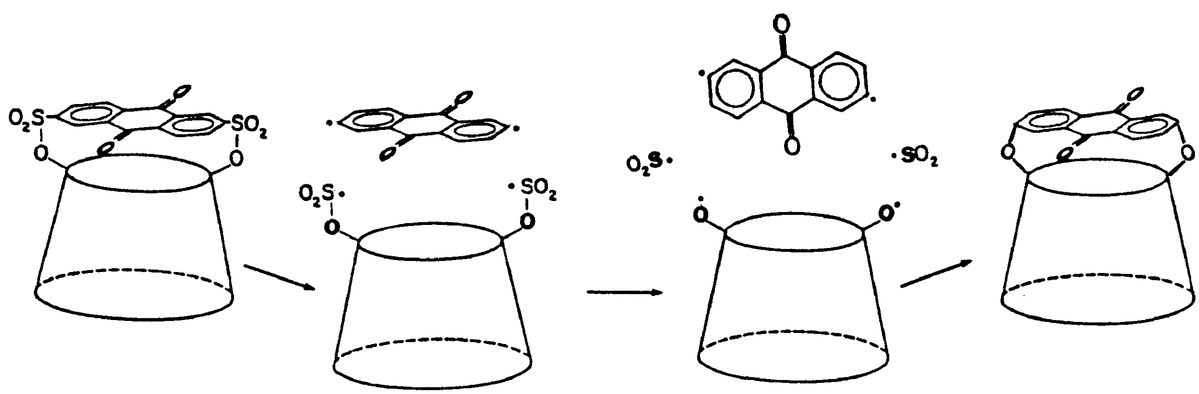
All synthetic schemes can be viewed as problems involving the preparation of the carbon framework, followed by the introduction, removal, or modification of functional groups. The general approach usually used for designing organic syntheses requires working backwards from the target molecule by a series of disconnections to produce a "synthon", or synthetic equivalent. The disconnections are imaginary operations aimed towards converting the target into possible starting materials; the synthons are generalized fragments, usually ions, which are often too unstable to exist and are replaced in the analysis by a functional equivalent, which ideally would be a standard reagent.

The obvious disconnection of the quinone cap from the cyclodextrin still leaves open the question of how the attachment will be made. What functional group would be most useful for reaction with the cyclodextrin's multiple alcohol units? Would it be more efficient to modify the cyclodextrin first and then attach the capping moiety? In this study, six target molecules, the disulfonic and dicarboxylic acid chlorides of the p-quinones,(Figure 3) are chosen in order to make use of information already gained from previous capping studies.

Theoretically, cyclodextrin in pyridine should exist in equilibrium with pyridinium cations and cyclodextrin with an indefinite number of alkoxide anions lining the primary rim. The exact position of this equilibrium is uncertain; however, the presence of a discrete number of potential nucleophiles on the cyclodextrin rim, as well as the excellent chloride leaving group on the modified quinone, suggest that the chosen method of attachment will guarantee some desired product. Typically, these reactions produce a modest, though reproducible yield for a given capped cyclodextrin. Consequently, focusing on the synthesis of the modified quinones should be a more useful pathway than the direct modification of cyclodextrins; the latter method generates characteristically low yields and difficult separations that plague investigators in this area. By deferring the cyclodextrin modification to the terminal step of the synthesis, it is hoped to minimize these problems.

When surveying the series of potential quinone caps, the synthetic utility of the disulfonic acid chlorides is uncertain. Sulfonate esters are known to be useful photoremovable protecting groups; therefore, sulfonate linked caps may undergo a C-S bond homolysis upon excitation,[24] making them less reliable than the carboxylate ester links. If the quantum yield of this process is significant, the radical pair formation could be followed by loss of SO_2 and either detachment of the cap, or recombination and subsequent attachment as an ether linkage.(Figure 8)

Figure 8. Photoremovability of Disulfonate Ester Linkage



Studies of this mechanism[25] among various sulfonic acid esters indicate that the reaction occurs from the excited singlet state, with a quantum yield for the alcohol formation ranging from 0.02 to 0.07, depending on the reaction conditions and the ester involved. The possibility of S-O bond homolysis as the first bond-breaking process has been ruled out as energetically unfavorable.[26] In the present study, the ability of the quinone radical to abstract a hydrogen from the aqueous solvent would affect the possibility of recombination, mediated by the speed of SO_2 extrusion. Even under the most favorable scenario, the diether linkage introduces a pair of electronegative atoms at points of attachment to the quinone ring, and reduces the spanning length of the cap, producing unpredictable effects on immediate photochemical developments.

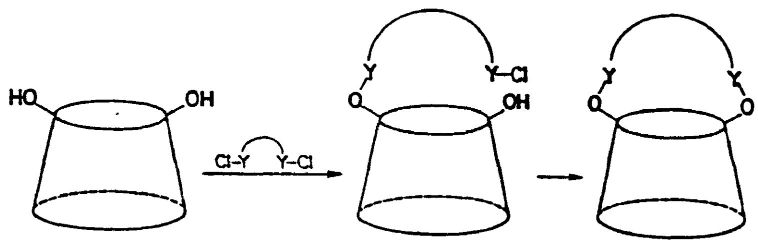
Whether or not these processes could compete favorably with electron transfer from included molecules should be individually determined for a given cap and guest, an approach which can not reasonably support a broad based catalytic study. Consequently, the proposed synthesis will focus on the carboxylic acid chloride derivatives; the more easily synthesized sulfonic acid chloride derivatives will serve to establish a preliminary methodology for separation and purification of quinone-capped cyclodextrins.

(B) THE CAPPING PROCEDURE

Before looking at the synthesis of the disulfonic and dicarboxylic acid capping agents, a general review of capping theory will help focus on the various reasons that a particular quinone might be preferred over another.

In the Tabushi model,[27] one of the acid chloride groups on the modified quinone attaches, by an addition-elimination, to a primary hydroxyl on the cyclodextrin, enforcing a "looper's walk" of the second acid chloride towards another hydroxyl group on the same face, to which it reacts, creating the bidentate linkage referred to as a rigid cap.(Figure 9)

Figure 9. Looper's Walk



Y = sulfonyl,
carbonyl

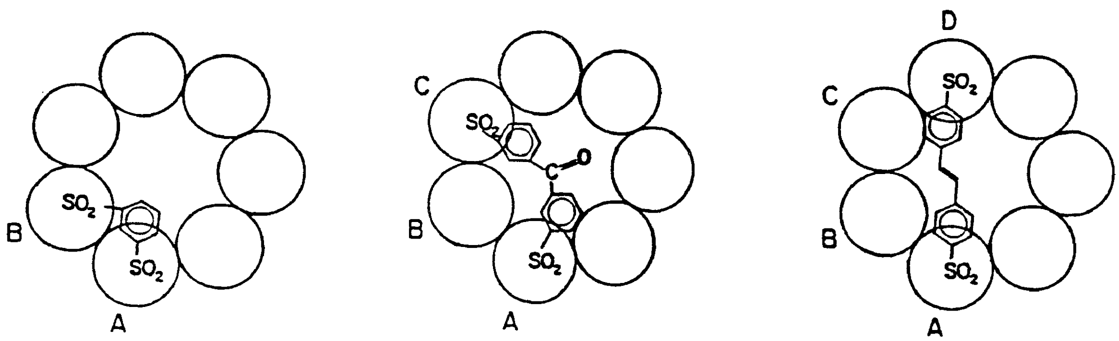
In the case of planar quinones, the position of the glucose monomer to which the second acid chloride attaches depends almost exclusively on the intramolecular distance between the reactive centers: the sulfur or carbon atoms on the acid chloride groups. An estimate of the distances between reactive centers of our six target molecules may be tabulated based on X-ray crystallographic data[28] and covalent bond distances.

Table 1. Intramolecular Reactive Center Distance

Target Molecules	Reactive distance(Å)
Benzoquinone-2,5-dicarboxylic acid chloride	5.9
-2,5-disulfonyl chloride	6.5
Naphthoquinone-2,6-dicarboxylic acid chloride	8.2
-2,6-disulfonyl chloride	8.7
Anthraquinone-2,6-dicarboxylic acid chloride	10.6
-2,6-disulfonyl chloride	11.1

We can correlate this information with quantitative studies done on other capping agents to predict the type of regiochemistry expected for the various quinone-capped cyclodextrins. After the initial attachment of the linking group, three discrete possibilities exist for the second linkage, shown in Figure 10 for caps used by Tabushi.

Figure 10. Regioisomeric Cyclodextrin Capping



a(A,B)[31]	b(A,C)[30]	c(A,D)[30]
planar	Z-oid/near perp./E-oid	planar
d=4.6Å	d=6-9.8Å	d=13.4Å

It is important to notice that the rotational ability of the primary hydroxyl groups, which can point the nucleophilic center away from the cyclodextrin cavity(Figure 1), can have dramatic effects on the effective distance between reactive sites on the cyclodextrin. Consequently, the distance between the A and C rings in Figure 10 actually ranges from 5.9-9.9Å,[29] implying that both of the anthraquinone caps in Table 1 are too long to bridge this distance, and should link strictly A,D. In the study with trans-stilbene-4,4'-disulfonyl chloride,[30] the A,D regioisomer distribution dominates, with some dependence on temperature and concentration. Analogies with anthraquinones cannot be drawn too closely; the presence of the fused rings and carbonyl groups change important physical considerations such as: interaction of the cap with the remaining primary hydroxyls, and solubility of the capped products in the reaction mixture.

A,B capping has only been observed in compounds with meta linking groups, such as m-benzenedisulfonyl chloride in Figure 10a.[31] None of the target molecules in this survey fall into that category, the shortest reactive center distance for the two benzoquinones falls just above the shortest calculable distance between the A and C glucose rings, and since below the shortest calculable A,D span(7.5Å), can be expected to link strictly A,C.

The fate of naphthoquinone caps is less clear, since their reactive center distances fall within the upper and lower limits of possible A,C attachment, but above the lower limit for A,D linkage. Here we could expect highly competitive A,C and A,D capping. For the molecules 1,1'-methylenebis-(benzene-4-sulfonyl chloride), the positional isomer distribution is non-selective.[27] The angular mobility around the methylene unit precludes any direct comparison with the naphthoquinones; however, the range of 9.0-11.0Å for the reactive center distance from the near perpendicular to the near coplanar conformations suggests that if there was a preference in distribution, the naphthoquinone reactive center distance would favor A,C.

Whenever we consider A,C linkage, we must also consider the additional possibility of dicapping; the somewhat skewed span of the cap would allow the entry of another planar cap for a D,F (or A',C') attachment. The driving force for this process could presumably arise from a entropically favorable decrease in the hydrophobic surface area which both caps maintain in contact with water. A,D capping would not have this competitive mechanism: in the absence of severe steric contortions by the cyclodextrin or its cap, this would require two molecules to occupy virtually the same space.

Whether or not the presence of two potential electron abstracting moieties would be favorable in the photophysical processes proposed for the capped complex is unclear, thereby reinforcing the utility of a survey approach to the synthesis, which allows us a choice of potential catalyst sizes. Other aspects of the product distribution will be addressed in **SEPARATION AND PURIFICATION.**

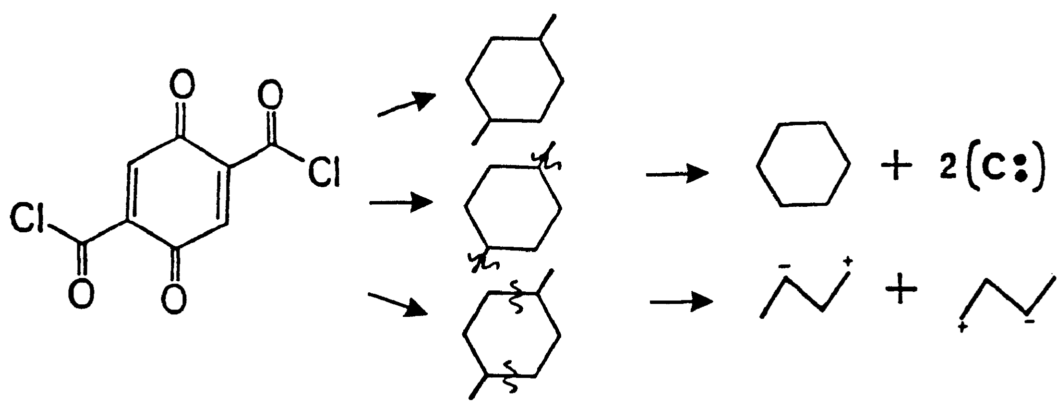
SYNTHETIC OVERVIEW

(A) DICARBOXYLIC ACID CHLORIDES

(1a) Benzoquinone

The simplicity and economy of the disconnection approach for p-quinones is clearly illustrated by using benzoquinone-2,5-dicarboxylic acid chloride as a target molecule. Identifying the carbon framework and performing the appropriate analytical operations gives three main synthetic pathways:

Figure 11. Benzoquinone Disconnections: Schemes A, B, C

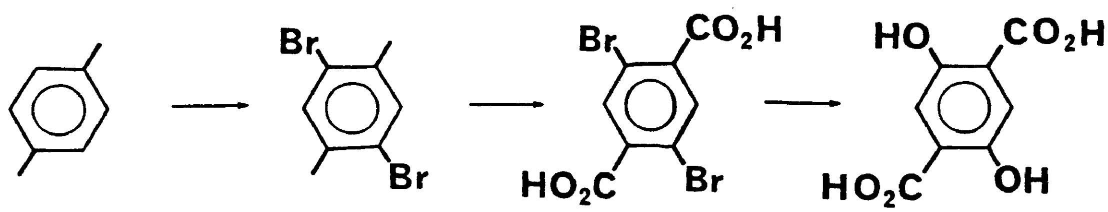


(A)
(B)
(C)

The disconnections give a choice in how to shift electrons, and that decision is usually dictated by our knowledge of organic reaction mechanisms.

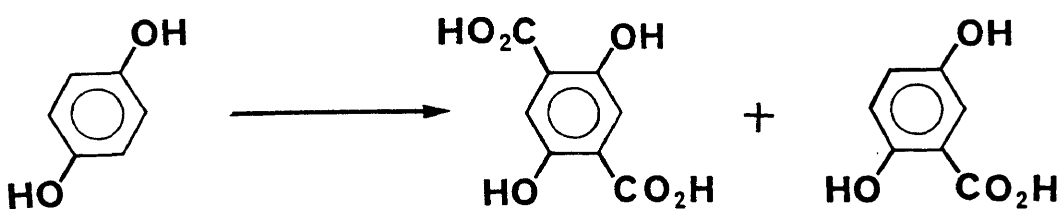
Scheme (A) shows that the carbon skeleton does not have to be broken down in these simple cases; one viable strategy ends with the intermediate diacid hydroquinone:[32]

Figure 12. Scheme (A)



This intermediate has also been reached, in a manner analogous to scheme (B), by direct addition of the carboxylic functionality to hydroquinone:[33]

Figure 13. Scheme (B)

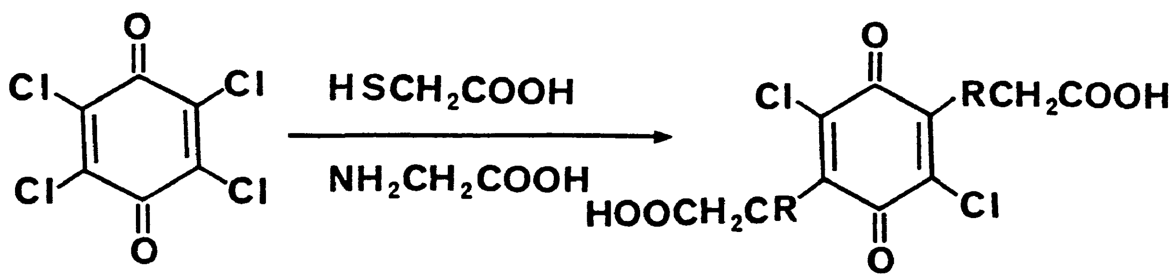


Further synthesis must follow the separation of mono- and di- carboxylic acid derivatives. Implicit in both of these pathways is the viability of oxidation of the hydroquinone to quinone, followed by activation of the diacid to diacid chloride.

Before choosing this, or any other pathway, the synthesis of the target molecule must take into account the conditions under which the photochemical studies of the proposed product complex is to take place. As mentioned previously, electronic excitation of benzoquinone in water is known to produce hydroquinone by initial abstraction of a proton from the solvent, presumably by the radical anion created in electron transfer. Stabilization of the radical anion could be accomplished by the introduction of two chlorine atoms to the carbon skeleton. The inductive withdrawal of electron density away from the carbonyl groups would arguably decrease the basicity of the oxygen atoms, thereby lowering the tendency for aqueous proton abstraction. Another benefit of this substitution lies in the raising of the excited state reduction potential of the quinone, making the potential cap a better photo-oxidant.[34]

Two related pathways to a chlorinated benzoquinone are analogous to scheme (B): nucleophilic substitution with a nitrogen compound such as glycine,[35] or with a sulfur compound such as thioglycolic acid,[36] on the carbon skeleton of benzoquinone as its 2,3,5,6-tetrachloro derivative.(Figure 14) Attending difficulties in these syntheses involve chromatographic separation of the isomeric mixtures, which often include the corresponding hydroquinones, and finding optimal reaction conditions; the latter is often difficult to maximize for a high yield of the desired derivative.

Figure 14. Scheme B: Chlorinated Derivatives(R = S,NH)



The presence of the heteroatom is also of dubious value, particularly with nitrogen addition: the non-bonding electron pair adjacent to the quinonoid ring could encourage electron transfer upon electronic excitation; charge-transfer complexes between quinones and nitrogen containing compounds are well documented.[37]

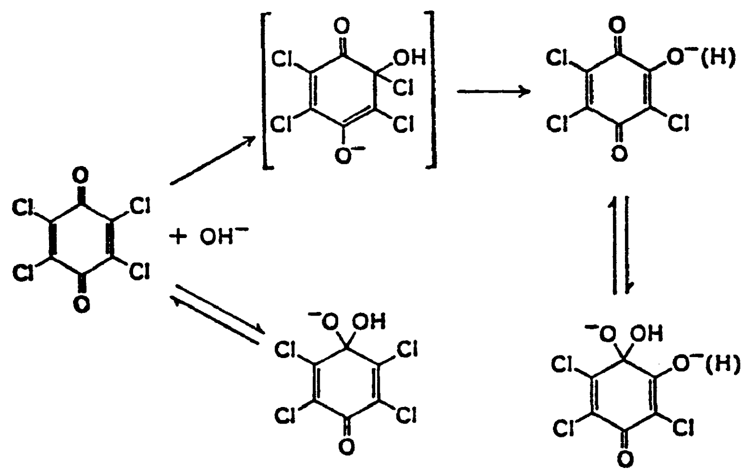
The availability of a reliable two-step synthesis of 2,5-dichloro-3,6-dicarbomethoxybenzoquinone[38] makes for a reasonable starting approach. In the proposed pathway to this diacid chloride precursor, chlorination occurs after the construction of the six-membered carbon ring via a double Dieckmann condensation of dimethyl succinate. (Scheme C) The product came out as the strongly enolised 1,4-dicarbomethoxy-cyclohexa-1,4-diene-2,5-diol, which upon rigorous chlorination gave the desired quinone.

Unfortunately, the ester hydrolysis did not proceed readily with standard techniques. Difficulties could have been anticipated, since aliphatic carboxylic acid groups that are beta to keto-functionalities are known to readily decarboxylate via a concerted intramolecular proton transfer with attendant six-electron shift. In the present case, such a mechanism would produce an allene on a six-membered ring, presumably a prohibitively strained species. This argument fails to consider the carbanion mechanism for decarboxylation, which proceeds through the deprotonated carboxylic acid and is enhanced by the presence of electronegative atoms on adjacent carbons.

Other problems may arise from the presence of the chlorine atoms. Studies of the behavior of 2,3,5,6-tetrachlorobenzoquinone in aqueous base show that the inductive withdrawal of electron density away from the carbonyl groups seems to facilitate the reversible addition of the hydroxide ion to the carbonyl carbon.[39] This argument parallels the one used for stabilization in gem-diol formation by the presence of adjacent electron-withdrawing groups.[40] The ring carbons that are points of chlorine attachment also serve as additional targets for nucleophilic attack.(Figure 15)

In the present synthesis, these last two chlorine-related complications preclude an easy route to the acid derivative with base hydrolysis. First, if two equivalents of hydroxide ion add to the carbonyl carbons, an electrostatic charge of -2 associated with the molecular orbital would make the approach of another two equivalents of hydroxide difficult. The experimental work in this project afforded mostly the return of starting material. Secondly, if we attempted the ester hydrolysis of the corresponding hydroquinone, the hydroxide ion could still add irreversibly to the ring carbons.

Figure 15. Hydroxide Addition to Chloranil



Acid-catalysed hydrolysis under various conditions also produced no isolable diacid quinone. Attempts at ester hydrolysis via an S_N2-like dealkylation with the strong nucleophilic agent LiI, led to uncharacterizable products. Destruction of the carbon framework would not be surprising, considering the distorting effect that the large, polarizable I^- ion would have as it approaches the chlorinated ring. Direct ester cleavage via PCl_5, which has been successful with alkyl salicylates,[41] failed here, resulting in the return of starting materials. Many other methods are known,[42] but most involve high temperatures that would facilitate decarboxylations. Although the failures of the attempted hydrolysis of the chlorinated dimethyl ester quinone do not demonstrate, or even suggest from the experimental evidence, that a decarboxylation mechanism is operative, the difficulties indicate that alternative approaches may be more synthetically useful.

One attempt to salvage 2,5-dichloro-3,6-dicarboxylic acid chloride benzoquinone as a capping agent could involve protection of the ring carbonyls as base-resistant ketal groups by treatment with ethylene glycol,[43] which can be removed later in acidic conditions after the base-catalysed hydrolysis. Unfortunately, we would still have the additional possibility of hydroxide attack on the chlorinated ring carbons, as well as decarboxylation once the quinone structure was restored. Conversion of the diacid to the diacid chloride before removal of the protecting groups would accomplish little; the acidic removal of the ketals could hydrolyze the acid chloride groups. This casual analysis does not even begin to address the difficulties involved in all protecting group methods: the extra steps and work-up involved.

Another attempt could involve a novel approach to the entire process of cyclodextrin capping: attachment of the dimethyl ester directly to the primary rim by transesterification. The alcoholysis of esters is an equilibrium reaction and must be shifted in the desired direction; the normal pathway involves aqueous acidic or basic catalysis, although several methods for transesterification under neutral conditions have been developed.[44] In the present context, the distillation of the low-boiling methanol as it is formed would be advantageous, although it is not clear that methyl would be a good leaving group under these conditions. The mechanism must be one of the acyl-oxygen fission routes: if alkyl fission takes place, the products are a dicarboxylic acid quinone and a dimethyl ether cyclodextrin, which are of no use in a capping pathway. The idea of capping cyclodextrins by transesterification has not been suggested in available literature.

Given the complications attending the presence of ring chlorines on the benzoquinone structure, which was originally proposed to stabilize the radical anion, it might be of some use to investigate the synthesis of benzoquinone-2,5-dicarboxylic acid chloride, since the postulated proton abstraction from water has not been tested under competitive conditions. If decarboxylation by the carbanion mechanism is a significant problem, the absence of the chlorines should make it less so. If decarboxylation by intramolecular proton transfer is a significant problem, then a route which avoids the fully protonated carboxylic acid could be useful.

The successful isolation of the potassium salt of 2-carbethoxycyclopentanone[45] gives us some indication of how to approach the synthesis: if we can dissolve 2,5-dicarbomethoxybenzoquinone in an ice-cold aqueous solution with two equivalents of KOH, we may be able to precipitate out the salt with ether, thereby avoiding an intramolecular proton transfer. Another isolation technique could be attempted with lyophilization:[46] freeze-drying the aqueous alkali solution and evaporating to dryness under reduced pressure. In either case, the dried salt could be suspended in benzene containing a trace of pyridine as catalyst, then treated at $0^{o}C$ with oxalyl chloride.[47]

In the present study, the availability of 1,4-dicarbomethoxy-cyclohexa-1,4-diene-2,5-diol as an intermediate in the chlorinated benzoquinone cap pathway led to attempts to convert this to the benzoquinone-dimethylester for use in the procedure just mentioned. Ester hydrolysis could also be attempted with the hydroquinone, giving the product from Fig 12. If we wish to avoid restoring the beta-keto position of the carboxylic acid, the next step involves the conversion of the diacid to the diacid chloride before oxidation of the hydroquinone to the quinone. In this scheme, methods of oxidizing the hydroquinone which also hydrolyze the acid chloride would have to be avoided.

Direct conversion of the rigid cis-dienol to the quinone was not viable with conventional techniques. Although the attempt to use chromic acid in the form of a Jones reagent[48] titration has been of some use for the oxidation of hydroquinones, it failed here. The general mechanism for chromate oxidation of primary and secondary alcohols is believed to involve the breakdown of an intermediate chromate ester[49] by scission of the alpha C-H bond, which is absent in both the aromatic and hydroaromatic forms under consideration here; therefore, analogies are difficult to make. A possible mechanism involves creation of a carbonium ion at the beta-keto position, followed by scission at the adjacent C-H bond.

Original efforts to oxidize the cis-dienol with $FeCl_3$ failed;[50] the standard conversion of the hydroquinone to quinone by this one-electron oxidant occurs through delocalized semiquinone radicals,[51] which would not be stabilized in the hydroaromatic dienol.

In searching for a method of aromatizing the cis-dienol, chemical dehydrogenation of hydroaromatics by high-potential quinones,[52] such as 2,3-dichloro-5,6-dicyano-benzoquinone, hold considerable promise. The mechanism is ionic; the first step consists of abstraction of a hydride ion by the quinone, followed by elimination of a proton from the substrate. The driving force of the reaction results from the conversion of both the quinone and alicyclic system into aromatic compounds.

In the present study, the Perrin and Perrin[53] suggestion of recrystallization from chloroform was used as a purification method, although this still does not rule out oxidant impurity as a reason for the failure of this approach.

The attempted oxidative aromatization by solid manganese dioxide was prompted by its success with similar compounds.[54] Although its oxidation potential is high, manganese dioxide is generally a mild oxidant under neutral conditions; however, the dehydrogenation of partially unsaturated carbocyclic systems has been accomplished under nitrogen in inert solvents. The mechanism, stoichiometry, reaction time and temperature for optimal yields are all unclear. Some experimenters[55] prefer in situ preparation of fresh MnO_2, as even the shelf-life of the oxidant has been shown to be a factor in the yield and identity of the generated product. Some preparative success has been achieved by azeotropic distillation from a benzene/MnO_2 mixture prior to addition of the reductant. In the present study, the procedure was modified by use of a Dean-Stark trap, and an observable volume of water was generated both before and after addition of the compound.

The failure of the oxidative aromatizations tried here may be due to reagent ineffectiveness; however, several other potential oxidants are still available. Ag_2O has been quite useful,[56] although it is often replaced by MnO_2 owing to its cost. If the cis-dienol is still to be the intermediate of choice, one of the more promising methods may rest in dehydrogenation over a metal catalyst, such as palladium on a carbon support.[57]

Alternative approaches are possible; Figure 12 and 13 gave pathways to the diacid hydroquinone, and here DDQ has been very useful, effecting oxidation through a charge-transfer intermediate.[58] If the conversion to the quinone could be achieved at room temperature, then any intramolecular proton transfer-assisted decarboxylation could be minimized. High potential quinones are useful in this respect by effecting hydroquinone oxidation at low temperatures, mainly as a result of their oxidation potentials.

Precipitation of the diacid salt of the quinone would allow an attempt at the oxalyl chloride treatment, as in the previously described method that had originally prompted attempts at aromatization and oxidation of the cis-dienol. Efforts to synthesize the benzoquinone-dicarboxylic acid chloride were abandoned owing to promising developments in parallel syntheses involving anthraquinones.

(2b) Benzoquinone(Extended links)

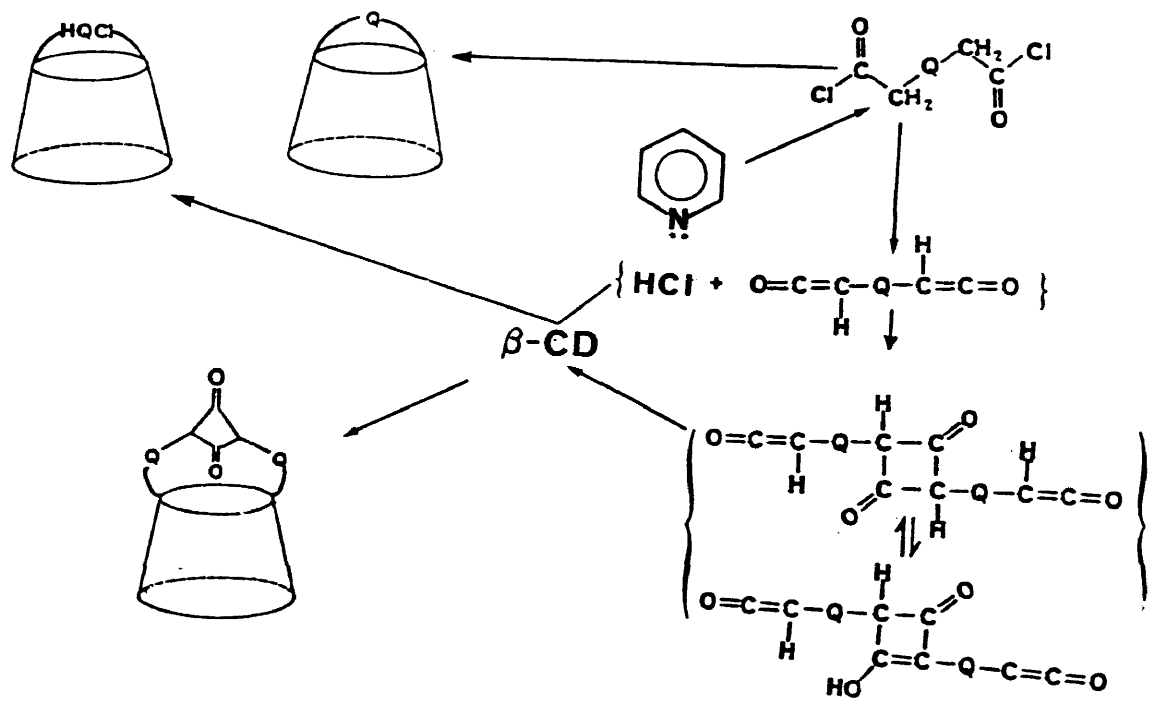
Figure 14 and Scheme B in Figure 11 suggest one more way of avoiding some of the difficulties involved in synthesizing carboxylic acid derivatives that are beta to the keto-functionality in the quinonoid dienone structure. Extension of the linking groups by introduction of a carbon between the intended acid chloride reactive center and the quinonoid ring would remove the beta-keto relationship, presumably circumventing any attendant decarboxylation problems.

The availability of a straightforward two-step synthesis of 2,5-dihydroxy-p-benzenediacetic acid[59] makes this a reasonable approach. The reaction conditions are critical: in the Michael condensation of ethyl cyanoacetate and p-benzoquinone(as in Figure 11, Scheme B), the benzoquinone behaves as an alpha,beta-ethylenic ketone; however, the enols formed from the quinones are stable as hydroquinones, they do not ketonize spontaneously. Some of the hydroquinone products are dehydrogenated in situ by an excess of quinone; therefore, the newly formed quinone undergoes a second Michael condensation. Great care must be taken to assure that the proper species at optimal concentrations are brought into contact with each other at the correct time; the procedure has been considerably improved by the original investigators.[60]

Dichromate oxidation of the diacetic acid hydroquinone product to the corresponding quinone was followed by conversion to the diacetic acid chloride by treatment with PCl_5 in benzene, thereby giving the target cap. In this last step, use of thionyl chloride, normally the reagent of choice owing to the extrusion of the easily removable gaseous products SO_2 and HCl, failed here, as it does with phthalic, succinic and aromatic hydroxy acids.[61] DMF or pyridine are often used as catalysts, but the results are still not consistently predictable. In this study, the IR and NMR of product mixtures showed some evidence of heteroatom incorporation at the alpha position, presumably a sulfur species.

The usefulness of the resulting product must be considered within the context of the conditions under which the capping reaction will be done. The pyridine-assisted alcoholysis of the diacid chlorides will introduce an additional complication when attempting to cap cyclodextrins with a diacetic acid chloride benzoquinone. The chlorine is known to facilitate abstraction of the alpha proton by amines such as pyridine, with consequent ketene formation and evolution of HCl. This will not by itself disqualify the diacetic acid chloride as a potential linking group; however, Figure 16 shows some of the competing reactions which will be set up under these conditions.

Figure 16. <u>Competitive Ketene Formation: Extended Links</u>



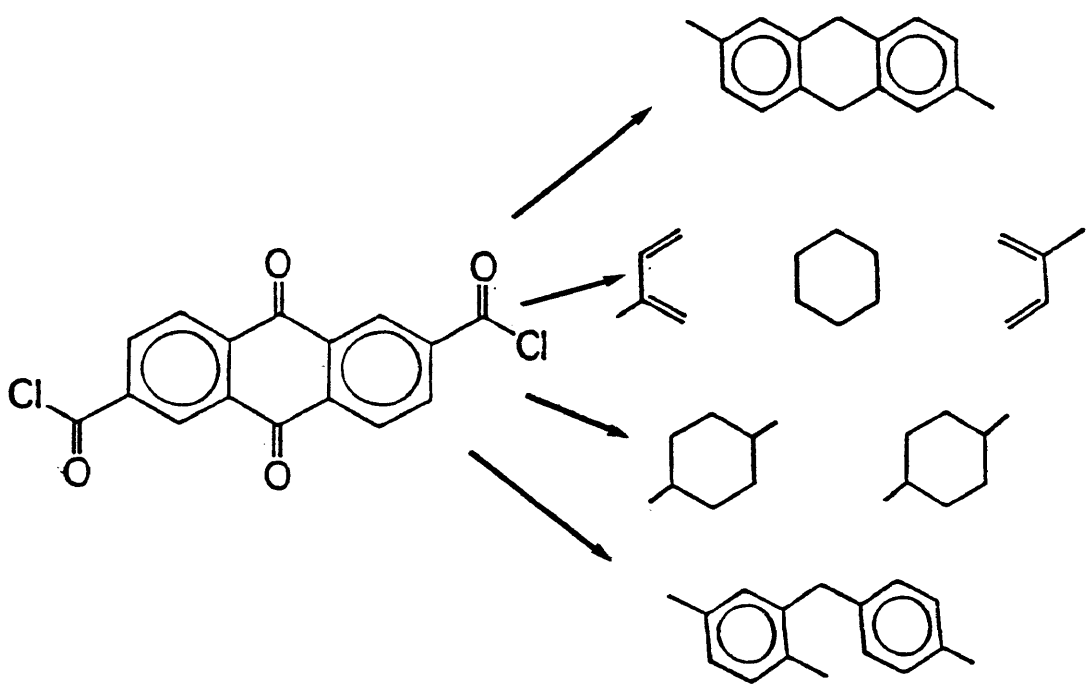
The great speed of ketene dimerization[62] suggests that a considerable amount of crosslinked and oligomeric products can be expected. The evolution of HCl will introduce additional complications if the pyridine is not excruciatingly dry: rearrangement of a quinone cap to a chloro-hydroquinone could occur, particularly if the acid by-product cannot be quickly removed from the reaction solution. Addition of 2,5-diacetic acid chloride benzoquinone to dry pyridine led to the evolution of a pungent smoke with immediate precipitation of a tarry material. When an expeditious transfer of the freshly synthesized capping agent was made to a prepared pyridine/cyclodextrin mixture, a similar event occurred.

Standard work-up of the crude product mixture gave C_{18} reverse phase bands coming off at 1:5 and 2:5 acetonitrile:water eluent concentrations, though attempted separation of individual bands on silica gel with various solvent systems failed to produce any characterizable products. ^{1}H NMR and IR did not rule out the possibility of some capped cyclodextrin; however, continued efforts along this synthetic route were made unattractive through contamination of normal and reverse phase columns with a sediment that could not be removed by standard elution systems.

(2) Anthraquinone

The disconnection of anthraquinone-2,6-dicarboxylic acid chloride suggests four pathways that may be useful.(Figure 17) Pathway (F) is the simplest; early investigations involved heating of benzoyl chloride at 120-140^{o}C with aluminum chloride to give a small amount of anthraquinone.[63] The yield is very low, and better results are claimed with benzoyl chlorides containing ortho-para directing groups: the action of aluminum chloride on meta-toluoyl chloride alone, in the same temperature range, supposedly gave 2,6-dimethyl anthraquinone. Although the yield and recovery of starting material are again too low to be of synthetic value, the synthesis of anthraquinone caps will focus around the production of the dimethyl derivatives, which can be oxidized by aqueous sodium dichromate to the dicarboxylic acid,[64] with functional group conversion to the diacid chloride by treatment with PCl_5.[65]

Figure 17. Anthraquinone Disconnections(Schemes D, E, F, G)



(D)

(E)

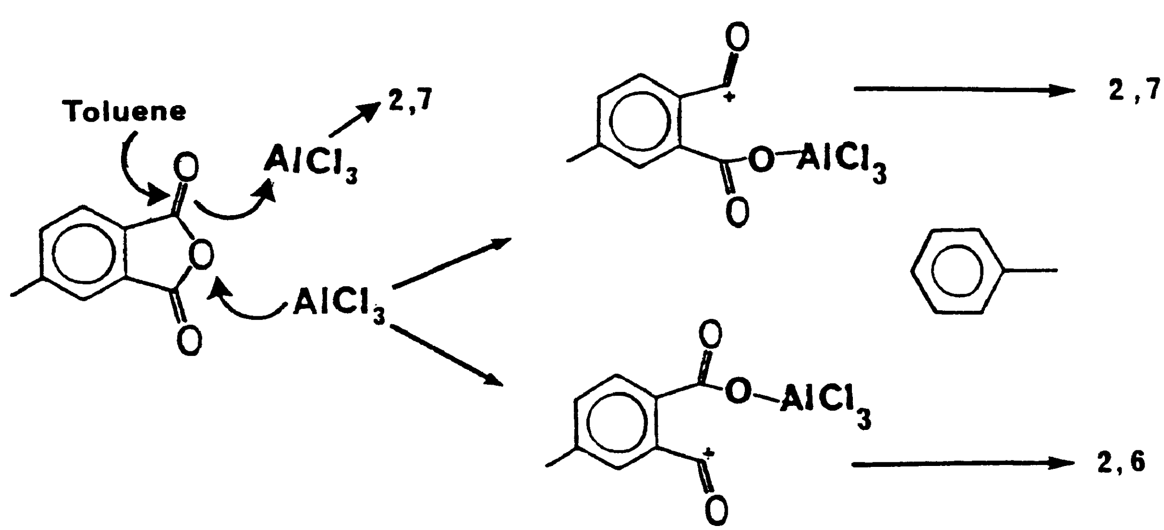
(F)

(G)

There are two generally accepted methods for synthesizing dimethyl anthraquinones: Diels-Alder cycloaddition of methylated 1,3-diene to benzoquinone, (Scheme E) and cyclization of a dimethyl-o-toluoyltoluic acid.(Scheme G) In the former we can expect a mixture of 2,6- and 2,7- dimethyl isomers of octahydroanthraquinone, which can be further dehydrogenated to the corresponding mixture of quinones.[66] Separation of the isomers involves tedious fractional recrystallizations:[67] ethanol preferentially solubilizes the 2,7- isomer, while glacial acetic acid partitions off the 2,6- isomer.

The need for isomeric work-up can supposedly be avoided if we follow a literature procedure for the cyclization method:[68] Friedel-Crafts addition of toluene to 4-methylphthalic anhydride to produce 3,4'-dimethyl-benzophenone-6-carboxylic acid. In the stem article, a quantitative yield of 2,6-dimethyl-anthraquinone upon ring closure is given as evidence for the nearly exclusive production of the acid isomer. No rationalization is given, although any reasonable explanation would begin with the directing effects of the methyl group in the anhydride. From Figure 18 we can see the result of a proposed methyl stabilization in the acylium ion mechanism.

Figure 18. Scheme G: Friedel Crafts



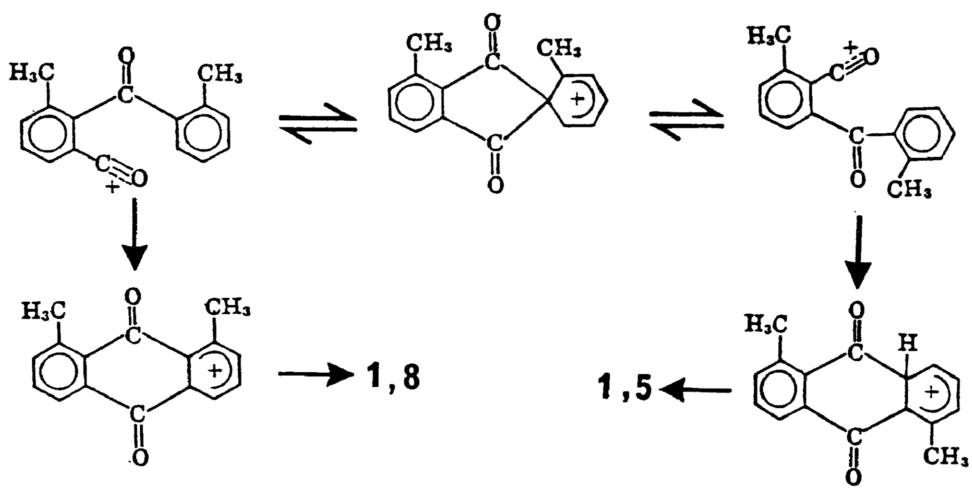
Whether the acylation proceeds by direct conversion of the anhydride to the acylium ion, or by polarization through oxygen, creating enhanced reactivity of the carbonyl carbon to nucleophilic attack by the acylating agent, the result is the same: if the methyl exerts an influence, the 2,7- isomer should be favored. In either mechanistic scheme, this presumes a significant field effect by the methyl over the width of the benzene ring; given the strength of the $AlCl_3$ reagent used, it seems doubtful whether a statistically meaningful effect on product distribution can really be expected. Repeating the literature procedure several times gave consistent, albeit approximate, equimolar ratios of the 2,6- and 2,7- isomers, based on weights gained from fractional recrystallizations.

Postulating a non-selective attack of the Lewis acid catalyst still does not address the possibility that positional scrambling occurs during cyclization of the substituted benzophenone with sulfuric acid. Such a rearrangement occurs with ring closures of both 3-methyl and 6-methyl-2-(2-methyl-benzoyl)benzoic acid,[66] resulting in mixtures of 1,5- and 1,8- dimethyl anthraquinones from either starting material.(Figure 19)

The Newman-Sandin mechanism for this Hayashi rearrangement[69] proposes an equilibrium pivoting of the toluyl ring during the attack of the acylium ion. Applying this rationale to the case of the 3,4' and

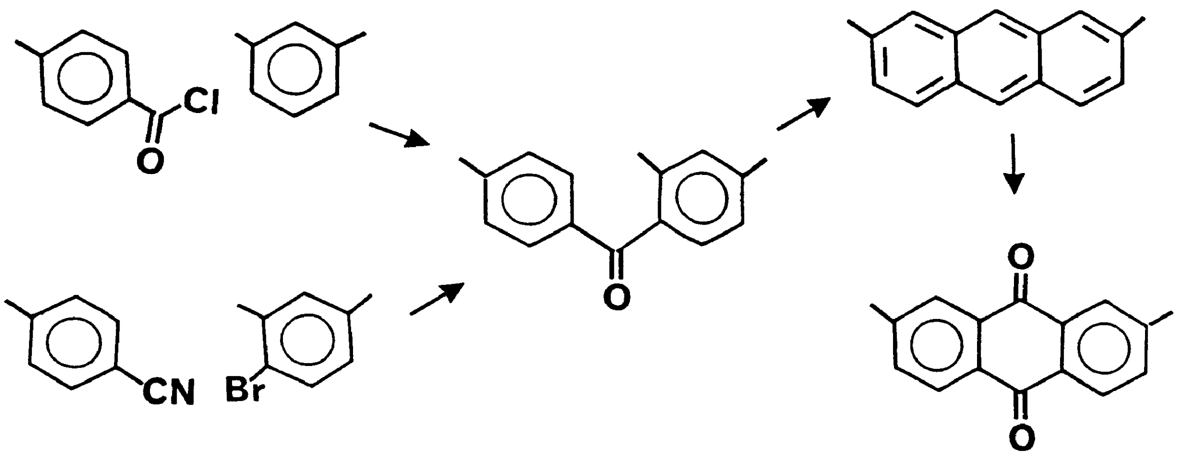
3,3'-dimethylbenzophenone-6-carboxylic acids would lead to no shift in the original isomer distribution: the methyl group in the toluyl ring should be para to the point of attachment, and swiveling about that point does nothing to change that relationship.

Figure 19. Newman-Sandin Mechanism: Hayashi Rearrangement



There are synthetic methods which exist that claim to selectively prepare for either 2,6- or 2,7-dimethyl anthraquinone; they may be retrologically arrived at by further disconnection of Scheme (D) to give a trimethyl benzophenone that is similar to the first step in Scheme (G). For the preparation of the 2,7- compound, the desired intermediate is 2,4,4'-trimethyl benzophenone, which can be synthesized by either hydrolysis of the ketimine formed by treating p-toluonitrile with the Grignard forms of 4-bromo- or 4-iodo-m-xlene,[67] or by Friedel-Crafts acylation of m-xylene with toluoyl chloride.

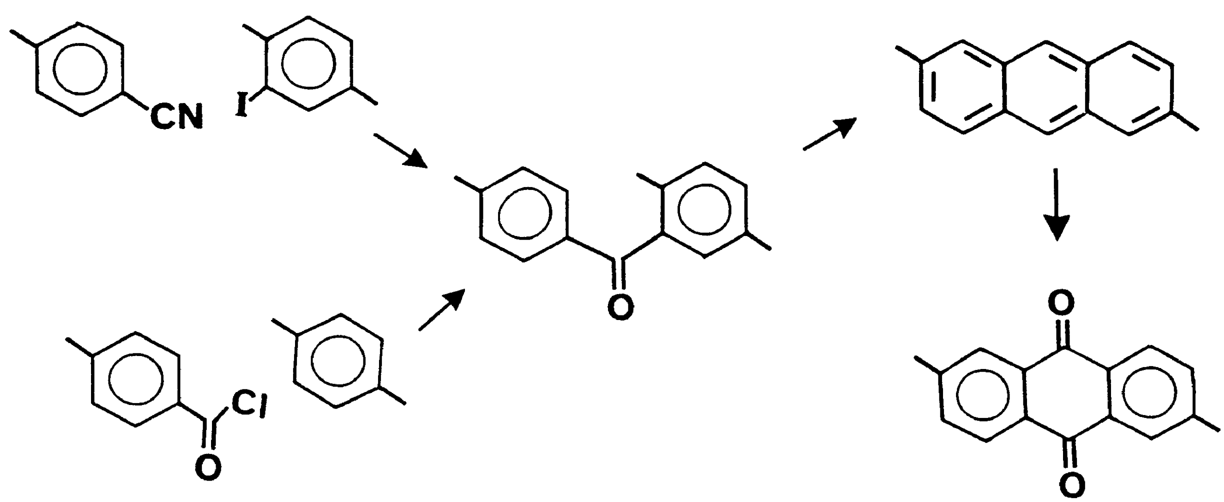
Figure 20. Scheme G: 2,7-Isomer



When the substituted benzophenone is maintained at its boiling point, it slowly loses water to form the 2,7-dimethylanthracene, whose nuclear carbons can be oxidixed to give the corresponding 9,10-anthraquinone. Similar schemes can be constructed for the preparation of the 2,6- isomer. (Figure 21) With these pathways, a synthetic scheme is used which avoids the ambiguity found in the Friedel-Crafts condensations; however, the yields are lower and nothing is gained in the work-up or number of steps.

The Friedel-Crafts approach taken in this study required the synthesis of the starting material 4-methylphthalic anhydride, mainly owing to its prohibitive cost. The literature synthesis starts with a picric acid catalyzed Diels-Alder addition of 26 g(0.383 m) of isoprene to 37.5 g(0.382 m) of maleic anhydride using 125 ml of benzene as a solvent.[70] 50 mg of the catalyst is used to give an 80% yield of the 1,2,3,6-tetrahydrophthalic anhydride. A first attempt to duplicate this gave much more modest yields; therefore, a single variable - the amount of picric acid - was chosen as the adjustable parameter.

Figure 21. Scheme G: 2,6-Isomer



2,4,6-trinitrophenol is highly explosive when dry and is shipped in 35% water; consequently, it is difficult to get an accurate weight of the active catalyst. Since this parameter is the one most open to experimental error, a consistent technique was used for draining the bulk water and weighing the resulting wet compound. The results, using various concentrations of catalyst with a constant amount of the other reagents, are given for four runs in Table 2.

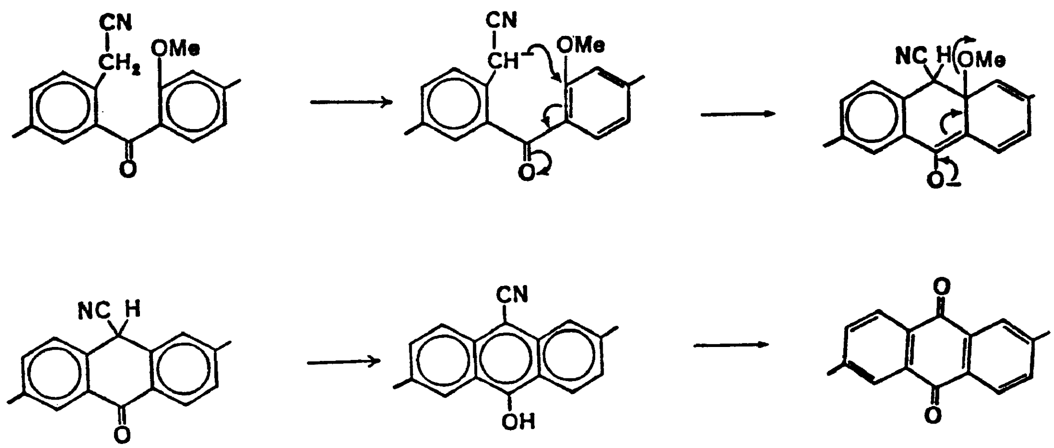
A plot of wet weight catalyst/unit amount of the limiting reagent(maleic anhydride) versus the % yield gives a linear fit with a correlation coefficient of 0.99. When a relative quantity of picric acid was reached that was approximately twenty times the implied literature value, the % yield began to level off.

Table 2. Picric Acid Catalysis	I	II	III	IV
Wet weight picric acid(g.)	0.16	0.43	0.59	0.69
Weight of product(g)	31.2	75.0	93.8	98.4
Wt. wet catalyst/ limiting reagent	0.91	2.46	3.37	3.93
% yield	35	59	74	77

In the o-toluoyltoluic acid pathway that was used in this survey, cyclization is theoretically hindered by the presence of an ortho-para directing group located meta to the site of cyclization,[71] which here would mean that a mixture of the 2,7- and 2,6- precursors from Figure 18 would, upon ring closure, give lower yields of both isomers of dimethyl anthraquinone. The absence of a quantitative IR of the dimethyl mixture circumvents any conclusions concerning how this would relate to the discussion of Figure 18 and the observed isomeric balance by bulk weight.

There are two ways to increase the yield of this pathway, neither of which were undertaken in this survey. First, the toluoyltoluic acid can be reduced, in either alkaline or acid conditions,[72] to a tolyltoluic acid, followed by routine cyclization to an anthrone and simple oxidation to a quinone. Second, the entire synthesis can be rerouted through o-benzoylphenylacetonitrile derivatives:[73]

Figure 22. Scheme D



The anthranol is formed here in 95% yield, compared to the 75% in this study's use of the o-toluoyltoluic acid pathway. The viability of the route depicted in Figure 22 depends on the availability of the starting materials, and the effects that the attendant methyl groups will have on the formation of the intermediate, and its consequent cyclization to either the 2,6- or 2,7- isomer.

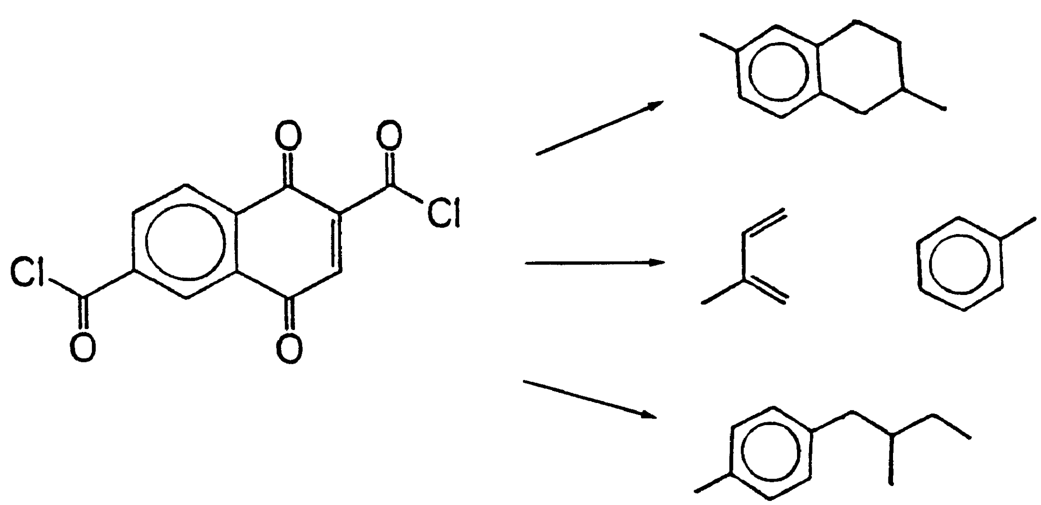
Whether or not we wish to consider the stereospecific synthesis of either 2,7- or 2,6-dimethylanthraquinone should depend on the relative advantages, with respect to capping, of one isomer over the other. The decrease of 0.13Å for the intramolecular reactive center distance of the former, as contrasted with the latter, still keeps the target adduct out of the range of competitive A,C/A,D capping; therefore, we could expect effectively identical regiochemistry. This does not consider potential differences in solubility between the isomeric caps or regioisomeric capped cyclodextrin in pyridine, which could potentially change any concentration dependent reactivity. The same differences in physical properties that allow separation by fractional recrystallization can imply distinct differences in their behavior in the reaction solvent. This aspect of the anthraquinone target molecules was not formally addressed in this study.

If we accept, as in this survey, that continuation of preliminary attempts to synthesize isomerically pure anthraquinone caps is not worth the time and effort involved, the Diels-Alder addition of isoprene to benzoquinone may be a more convenient way to approach the problem. Under the proper reaction conditions, the cycloaddition step does not stop at the naphthoquinone stage,[74] but proceeds to the isomeric mixture of octahydroanthraquinones. Later studies[75] suggest the little used possibility of running the reaction in a reducing solvent such as nitrobenzene, circumventing the need to dehydrogenate an intermediate octahydro-derivative. Yields would be lower than in the Friedel-Crafts synthesis; however, an extra step is avoided and work-up is simpler. When comparing the two pathways, 4-methylphthalic anhydride should logically be considered as a starting material. After initial separation of the 2,6- and 2,7-dimethyl isomers by fractional recrystallization, the remaining functional group transformations were done on the sublimated bulk mixture.

(3) Naphthoquinone

The carbon skeleton of naphthoquinone-2,6-dicarboxylic acid chloride suggests three discrete ways to devise the synthesis. (Figure 23)

Figure 23. Naphthoquinone Disconnections(Schemes H, I, J)



(H)

(I)

(J)

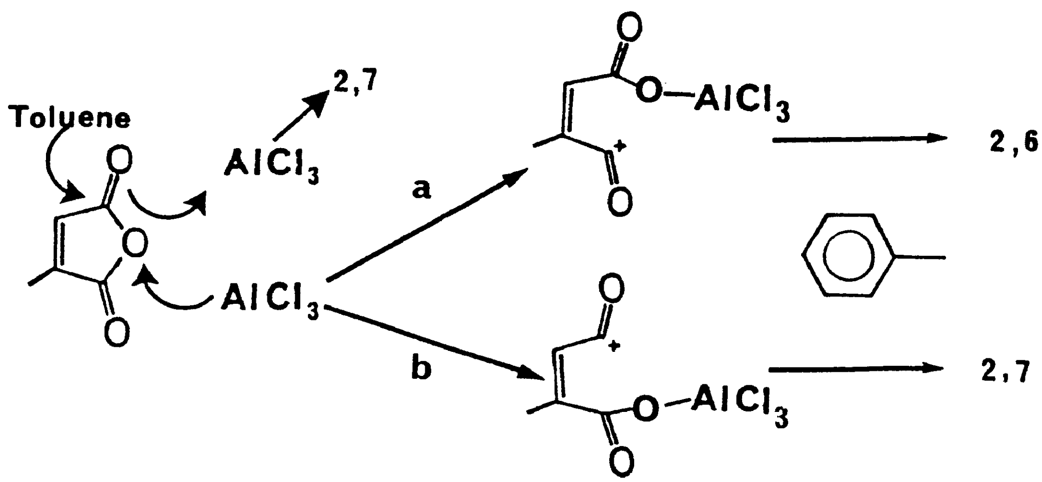
The target molecule is again approached from its dimethyl precursor; in Scheme (H) chromate oxidation of a pair of the nuclear carbons on naphthalene proceeds easily, since oxidation is an electrophilic attack, and the methyl groups activate either ring. Easily available commercial dimethyl naphthalene comes as a mixture of isomers, the difficulty in the separation process being reflected in the prohibitive cost of the pure isomers.

A single disconnection of the benzenoid ring in the target molecule(Scheme I) suggests a method that can be analyzed from a similar perspective as the Friedel-Crafts synthesis of dimethylanthraquinone: the condensation of citraconic anhydride with toluene to produce an intermediate β-aroylacrylic acid, which can then be cyclized to the corresponding naphthoquinone. As with the anthraquinone cap, the dimethyl derivative is sought; however, in this synthesis the additional problem of a mono-decarboxylation needs to be addressed. Under the autoclave conditions of heating at constant volume with the resultant increase in pressure, the extrusion of CO_2 is entropically unfavorable. Assuming that this process would allow us to oxidize both methyl groups, the regeneration of the diacid by precipitation of the dicarboxylate salt could be done at low temperatures. Redissolution of the solid in aqueous base could be followed by lyophilization, then treatment with oxalyl chloride at $0^{\circ}C$.

The isomeric product distribution expected from the condensation of citraconic anhydride and toluene can be rationalized along lines similar to the logic used in

Figure 18.

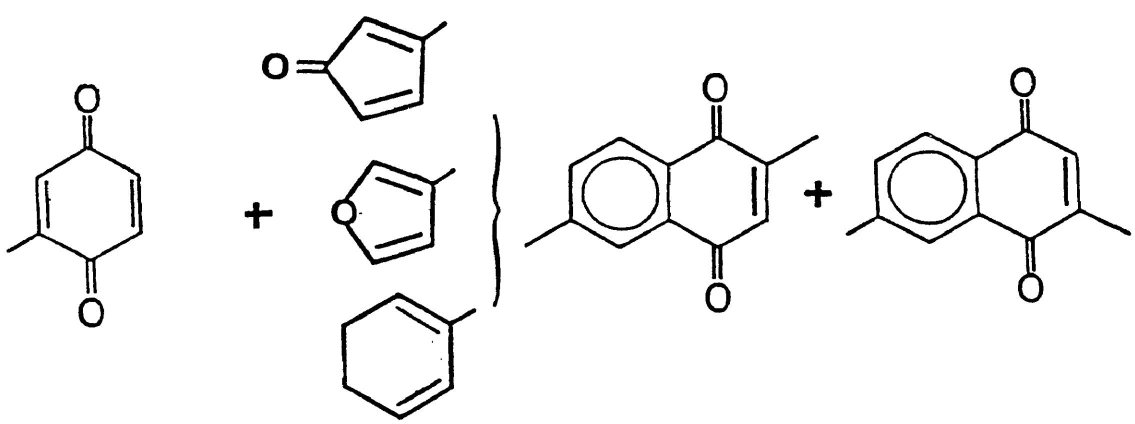
Figure 24. Scheme J: Friedel Crafts



Early studies[76] claim the formation of β-toluoyl-α-methylacrylic acid almost exclusively, which would favor the 2,7- isomer upon cyclization. Rationalizing this from an inductive effect of the methyl group is not clear: if we assume a near statistically equal distribution of acylium ions after a non-preferential attack of the Lewis acid catalyst, the methyl group could be seen as a stabilizer of the cationic enone system in pathway 24b, even though in pathway 24a it is in closer physical proximity to the positive charge. In either case, the cyclization can theoretically be accomplished in one step by the addition of excess $AlCl_3$ to the condensation reaction, or in two steps by the treatment of the acrylic acid in an $AlCl_3$:NaCl melt at 200°;[77] however, the results are not consistent, and the evidence not convincing. In this study, the former method was tried, which upon multiple column chromatography with various mobile and stationary phases, did not lead to a characterizable product.

A double disconnection of the benzenoid ring in the target molecule(Scheme I) suggests that a Diels-Alder annelation could be a versatile synthetic method: the methyl group provides deactivating electron density to one side of the dienophile, allowing reaction of the other side of the ring to a variety of dienes(Figure 25):

Figure 25. Scheme I: Diels-Alder



including isoprene, which was used in this study. The main reason for preferring one diene over another would be in the ease of work-up, yield, or distribution of the isomeric products, which can also include isomeric hydroquinones. The Diels-Alder reaction of isoprene and toluquinone proceeded quite efficiently; the resulting tetrahydroaromatic mixture of 2,6- and 2,7- isomers was fully aromatized by treatment with MnO_2 in benzene. Unfortunately, the attempt to oxidize the non-separated dimethylnaphthoquinones gave a mixture of by-products whose ^1H NMR showed evidence of paramagnetic material.

It is of some interest to note that the presence of metal cationic species has been known to facilitate the carbanion mechanism for decarboxylations of B-keto carboxylic acids.[78] It is not clear whether this is possible in the chosen autoclave conditions; this particular oxidation requires a 1:1 stoichiometry of dichromate to methyl group:

$$Ar\text{-}CH_3 + Na_2Cr_2O_7 \dashrightarrow Ar\text{-}CO_2Na + NaOH + Cr_2O_3 + H_2O$$

The sodium hydroxide formed retards the oxidation; therefore, up to 50% excess oxidant is used as a buffer:[64]

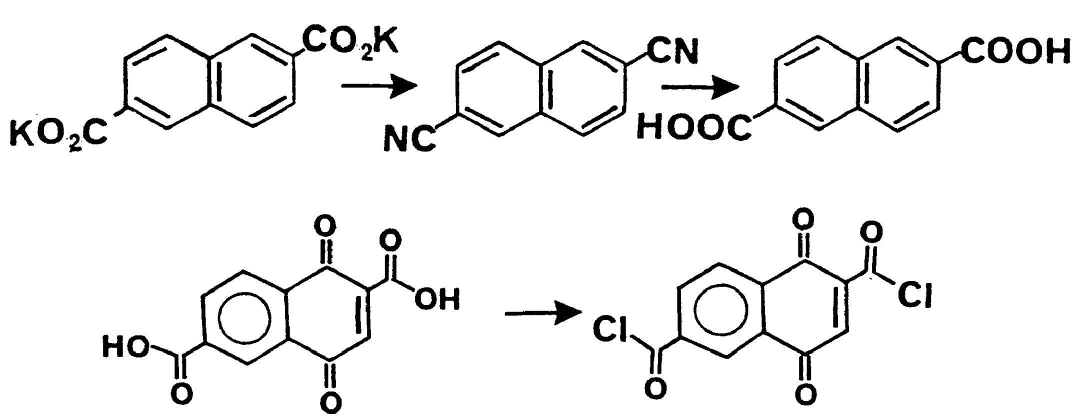
$$Ar\text{-}CH_3 + 1.5Na_2Cr_2O_7 \dashrightarrow Ar\text{-}CO_2Na + Na_2CrO_4 + 1.5H_2O + Cr_2O_3$$

Buffering has also been effected by CO_2,[79]
and the change of pH from 4-5 to 7-8 in this study helps rationalize these equations. Scrupulous cleaning of the autoclave was directed against contamination from previous runs. The explanation of the paramagnetism of the ^1H NMR remains problematic, although the basic dienone

structure is known to form charge-transfer complexes with a variety of substances, and the mechanism of aromatic alkyl side chain oxidation is believed to involve free radicals.[80] In the present study, the naphthoquinone synthesis was abandoned at this stage, although the precipitation of material upon acidification of the product liquor is at least indirect evidence of some carboxylate salt having been formed, possibly only a mono-carboxylate. Earlier studies[81] claim the formation of naphthoquinone-2-carboxylic acid, although a clean isolation of a quantity of the product was not accomplished.

Another possible method of synthesizing the capping agent[82] lies in the availability of the 2,6-dicarboxylate salt of naphthalene.(Figure 26) The advantage of this

Figure 26. Scheme H



method over the oxidation of the methyl groups in 2,6-dimethyl naphthoquinone lies in the lower reaction temperatures necessary to elicit an oxidation of the nuclear carbons, and therefore a decreased facility for decarboxylation of the quinone ring. This may not be a useful observation unless, when compared with the dimethyl derivative, the diacid form does not significantly deactivate the ring towards oxidation, nor cause solubility changes that interfere with subsequent isolation and purification.

(B) DISULFONIC ACID CHLORIDES

(1) Anthraquinones

The synthesis of anthraquinone-2,6-disulfonyl chloride is trivial owing to the availability of the disodium salt, which can be treated with PCl_5 for a reasonably straightforward work-up. The 1,5-isomer is synthesized in similar fashion; the intramolecular reactive site distance makes for an indistinguishable looper's walk, although the closer proximity of the linking groups to the quinone carbonyls anticipates some differences in physical properties, notably the electronic spectra. Both of these isomers are adequately covered in the experimental section.

(2) Benzoquinone

As in the case of the dicarboxylic acid chlorides of benzoquinone, the synthesis should first address the feasibility of the chlorinated derivative, 2,5-dichloro-benzoquinone-3,6-disulfonyl chloride, which could arguably decrease the photoinduced proton abstraction capability of the cap in an aqueous system. In a manner analogous to Figure 14, the hydroquinone precursor is synthesized by the sulfonation of chloranil.[83] Oxidation of this chlorinated aromatic is probably best achieved by molecular oxygen with a Cu/pyridine catalyst;[84] other chemical methods have disadvantages owing to the reactive site opened up by the presence of the chlorine atoms, and the additional complications introduced by the sulfonyl groups. Activation of the sulfonic acid could again be achieved by PCl_5.

If this approach should fail, or if the chlorinated derivative is not desired or necessary, the availability of 2,5-dihydroxy-1,4-benzenedisulfonic acid dipotassium salt allows for a direct pathway to another target molecule. Conversion to the disulfonic acid can be accomplished by simple elution down an acidic cation exchange column. 1,4-benzoquinonesulfonic acid may supposedly be achieved by dichromate oxidation of the hydroquinone,[85] with functional group conversion again accessible through PCl_5. Oxidation of the hydroquinone disulfonic acid has also been claimed to have been accomplished by use of manganese dioxide.[86] In the present study, the latter method gave some evidence of partial success, and treatment of the product with PCl_5 gave a small amount of material with evidence of sulfonyl chloride stretches in the IR. Isolation of a quantity of characterizable material was difficult, owing to the solubility of species in both organic and aqueous solvents. The possibility of mono-functionalization was a recurring problem for these type of syntheses, leading to changes in physical properties that complicate efficient separations. The dichromate oxidation may have failed for similar reasons; the literature source concerned the mono-sulfonic acid derivative of hydroquinone; the corresponding quinone may be less water-soluble than the diacid, and it is therefore easier to extract a modest yield from an aqueous system.

(3) Naphthoquinone

Pathways to the 2,6-disulfonyl naphthoquinone derivatives are not well investigated. Two logical methods to the desired product include: a chromate oxidation of a pair of nuclear carbons in a 2,6-disulfonyl derivative of naphthalene; or a disulfonation of naphthoquinone. The 2,6-disodium salt of naphthalenedisulfonic acid is readily available, and conversion to the disulfonic acid by ion exchange could be followed by chromic anhydride treatment and salting of the solution to precipitate out the diacid quinone, which may be less water-soluble than the corresponding benzoquinone.

Sulfonation of naphthoquinone remains less clear as a possible synthetic pathway. It is well known that the sulfonation of naphthalene proceeds to equilibrium at 160°C, leaving primarily beta isomer; at 80°C, the alpha isomer predominates. Classical arguments based on resonance structures and steric interactions adequately explain the differences between thermodynamic and kinetic control of the monosulfonate product distribution. Owing to the symmetry of the naphthalene molecule, only two chemically different positions exist for the first electrophilic aromatic substitution. The second sulfonation offers more discrete possibilities, and the distribution of products is difficult to predict with resonance arguments, and just as difficult to control with temperature manipulation. The shifting of sulfonate groups is not uncommon, and serious problems exist in the separation of isomers.[87]

By analogy, the second sulfonation of naphthoquinone could be open to similar problems. Primary sulfonation occurs at the position beta to the carbonyl;[88] depending on conditions, the second substitution can occur at any of the carbons on the other rings, except those common to both rings of the fused structure. Systematic studies are wanting.

In this survey, only the disulfonyl chloride of anthraquinone was used in an actual capping scheme, although the benzoquinone and naphthoquinone derivatives would hold some promise if the photoremovability of the sulfonate ester linkages is not a significant problem.

SEPARATION AND PURIFICATION

The difficulties involved in work-up of a crude mixture of capped cyclodextrins partially arise from the variety of products we can expect from the simple Tabushi model. Before tackling this problem, we should address the known effects of the reaction parameters of temperature, time, stoichiometry and concentration on product distribution. Tabushi and coworkers varied several reaction parameters while attempting to characterize the regiospecific A,C and A,D disulfonate capping of cyclodextrin.[30] Table 3 gives

Table 3. Capping Reaction Parameters

cap	T, ^{o}C	#	[cap]10^{-3}M	[CD]10^{-3}	t,hr.	%yield	A,C:A,D
10b	25	1	15.0	17.6	5	53	75:8
	60	2	45.8	17.6	1		35:2*
		3	15.0	17.6	1	40	94:6
10c	25	4	2.2	2.6	7	30	11:81
		5	15.0	17.6	7	33	24:57
		6	37.4	44.0	7	33	30:50
	60	7	45.8	17.6	1		small
		8	18.0	18.0	2	20	0:100

*A,C/A',C':A,C.

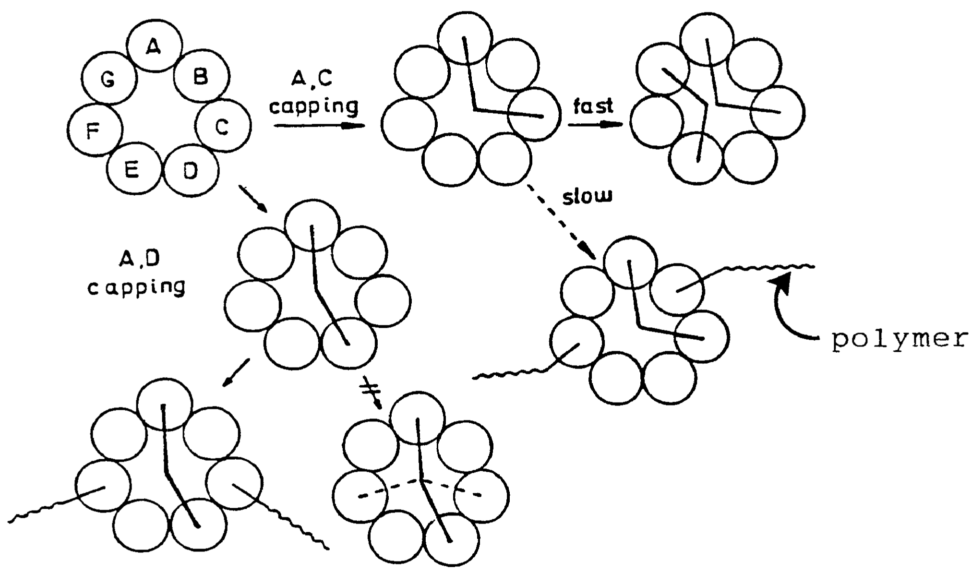
selected results for studies which included the capping reagents in Figure 10b and 10c.

The stoichiometry was varied by using 0.8-2.6 equivalents of capping agent, with reaction conditions ranging from 5-7 hours at $25^{o}C$ to 1-2 hours at $60^{o}C$. Concentration of both cap and cyclodextrin were kept on the order of $10^{-2}M$, with only trans-stilbene-4,4'-disulfonyl capped cyclodextrin showing regioisomeric concentration dependence: decreasing dilution showed increasing ratios of A,C to A,D capped cyclodextrin.

No reasoning is given for the chosen values of the reaction parameters, nor for the anomalous concentration dependence of the trans-stilbene derivative. Detailed kinetic and mechanistic studies are wanting; therefore, for the purposes of the present synthetic study, reaction conditions were kept within the ranges used by Tabushi, and variations were only analyzed from the point of view of gross effect on yield or work-up.(Table 5; Experimental)

How can we use the meager information given in the Tabushi model to interpret the Table 3 results, and thereby anticipate the type of products to expect from various reaction conditions when anthraquinones are used as capping agents? We can extend the intramolecular reactive center distance argument used in **SYNTHETIC STRATEGY** to include a more general scheme for the positional isomer distribution of capped cyclodextrins. Figure 27 shows the competitive capping to be expected from intramolecular reactive center distances within the ranges defined by the examples given in Figure 10b and 10c.

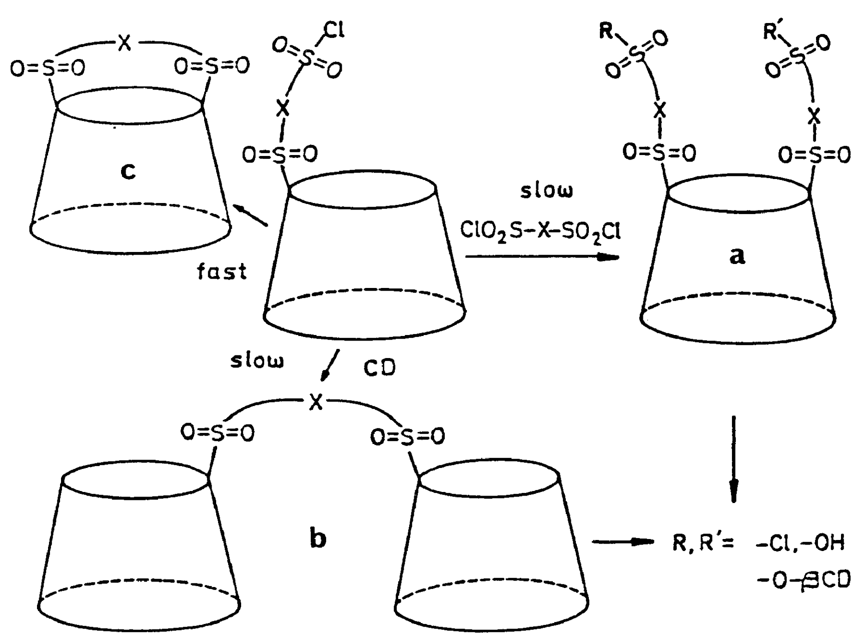
Figure 27. Tabushi Model: Positional Isomer Distribution



Three things can be immediately recognized from this mechanistic scheme: the tendency for quick dicapping with regiospecific A,C attachment; the lack of facility in the A,D dicapping mechanism; and the slow build-up of polymeric material after mono-attachment by either the A,C or A,D routes. The first two points were rationalized on page 26, although the impact that competitive A,C/A,D monocapping has on product distribution and the consequent work-up still needs to be addressed. Before attempting to resolve a regioisomeric mixture; however, undesirable by-products should be eliminated from the sample.

The polymeric material shown in Figure 27 can be easily removed from the crude reaction mixture: after the pyridine is evaporated and the residue dissolved in a minimal volume of water, dropwise addition to an acetonitrile:water solution will precipitate out the less soluble polymers and oligomers. Longer reaction times could favor the build-up of polymeric material relative to single or double capping, depending on the intramolecular reactive center distance and the presence of other products in the reaction mixture. Figure 28 shows the primary sources of impurities we can logically expect in a capping reaction.[30]

Figure 28. Tabushi Model: Capping Reaction Impurities



Clearly, every product in the reaction mixture must arise from the first mono(sulfonate/sulfonyl) chloride in the proposed mechanism. The presence of two pathways competing with looper's walk - intermolecular condensation in 28b and monodentate dicapping in 28a - suggest a reasonable build-up of by-products that may not be removed by simple precipitation. What is not clear is how efficient these pathways are under various reaction conditions.

On the basis of concentration insensitive regiochemistry, Tabushi claims that intramolecular capping(28c) is more effective than intermolecular oligomerization(28b). Crude mixtures of various A,C and A,D capped cyclodextrins and di(sulfonate/sulfonyl chlorides[28a]) were converted to their corresponding bis(sulfides) with NaSPh-t-Bu; the resulting mixture was separable by HPLC through a carbohydrate column.[30] For various initial concentrations of cap and cyclodextrin, maintaining a stoichiometry of 0.85 equivalents of capping reagent, the resulting ratios of the A,C- and A,D-bis(sulfides) remained constant.

Figure 28 shows that the bis(sulfides) represent two distinct products: capped and difunctionalized cyclodextrins. Since it is highly unlikely that difunctionalization proceeds with the same regiochemistry as capping, it must be that difunctionalization has a minimal effect on overall product distribution. If this argument holds, concentration insensitive regiochemistry would imply that looper's walk is more favorable than intermolecular condensation.

It may be important to note that this quantitative study involved the decantation of the supernatant reaction mixture from the waxy residue instead of evaporation of all the solvent; therefore, the non-terminal cyclodextrin units of the higher molecular weight oligomers or polymers were not a part of the measurement of the A,C and A,D-bis(sulfide) distribution, shown as % yield in Table 3, column 5. As oligomers and polymers form they precipitate out of solution, decreasing the concentration of both cyclodextrin and cap. Assuming an anhydrous environment in which sulfonate/sulfonyl chlorides are not being hydrolyzed to sulfonate/sulfonic acids, longer reaction times favor continued build-up of insoluble materials, though at a decreasing rate as increasing dilution makes it more and more difficult for the molecules to find each other in solution. Capping should decrease much more quickly than intermolecular oligomerization, as the tethered monosulfonate/sulfonyl chloride has only to swing across the primary face of the cyclodextrin in order to find a reactive hydroxyl to attach to, and this should not be dependent on solution concentration.

It is also not clear how the anomalous concentration sensitive regiochemistry of trans-stilbene-4,4'-disulfonyl capped cyclodextrin(Table 3, #4-6) should be interpreted:

the intramolecular reactive center distance most closely approximates the anthraquinones used in Table 5, where a dramatic decrease in yield follows with increasing concentration. For the dicarboxylate linked anthraquinone, this may simply be a function of the low solubility of the cap in pyridine. Multiple runs with systematic variation of selected reaction parameters is needed in order to make tentative judgements.

Additional possibilities exist for by-products: tri(sulfonate/sulfonyl) chloride cyclodextrins, single caps with mono- and di(sulfonate/sulfonyl) chloride substitutions, as well as a number of included cap variations on the themes already mentioned. Most of these compounds may be chromatographically removed by taking advantage of differences in the partitioning between various mobile and stationary phases. Of the various solvent systems used in Table 6(Experimental), acetonitrile:water seems to be most useful in resolving the combinations of hydrophobic and hydrophilic areas in the possible macromolecular derivatives of cyclodextrin.

Starting materials such as cyclodextrins, disulfonic or dicarboxylic acid chlorides and their corresponding diacids, organic ions such as disulfonates or dicarboxylates, as well as pyridinium hydrochloride, are easily separated from the crude reaction mixture. Anionic and cationic exchange resins remove the organic ions;

reverse phase C_{18} can partition off the cyclodextrins, diacid chlorides, diacids, and inorganic ions left from the exchange resin treatment.

Some of the product distribution will depend on the stoichiometry of the reaction. From Table 3 we saw that 0.85 equivalents of benzophenone-3,3'-disulfonyl chloride gives A,C capping almost exclusively, with little formation of doubly capped cyclodextrin; however, 2.6 equivalents give mostly A,C/A',C' moieties, with very little single capping. From Figure 27b and the page 26 reference, we could question why no dicapped material is formed with a slight deficiency of capping agent. Although A,C dicapping has been argued to be thermodynamically favorable, kinetically it could be slower than monofunctionalization and a subsequent looper's walk.

The use of silica gel with isocratic elution by 6:1 acetonitrile:water gives separation of doubly and singly capped cyclodextrins with R_f's of 0.6 and 0.2, respectively, for disulfonyl derivatives. The presence of freely spinning "caps" would give the additional possibility of interaction with other modified cyclodextrins via inclusion complexes. The least we should expect would be a great deal of band broadening associated with the statistical distribution of molecular motions and intermolecular interactions of macromolecules that possess a peculiar mix of hydrophobic and hydrophilic areas.

An attempt to develop a dicapped cyclodextrin with minimal separation difficulties could use some of the information gained from other studies. A,C/A',C' capping has been demonstrated using an excess of benzophenone-3,3'-disulfonyl chloride, and conversion to a tetra-amine derivative can be accomplished by known methods, followed by persilylation of the C_2-OH groups with t-$BuMe_2SiCl$ to solubilize the cage molecule in organic solvents.[89] The regioisomers can then be effectively separated by column chromatography with aprotic solvents, and regenerated in the original tetra-amine form by removal of the protective groups. The purified product could then be treated with a 2+ stoichiometric excess of 2,5-diacetic acid benzoquinone, with a dehydrating agent added to encourage amide links. Dicapped material of known regiochemistry would be created, although we still would require removal of oligomeric material, organic anions and cations, and unreacted cyclodextrin. Some dicapped A,D/A,'D' material might be expected, owing to the length and flexibility introduced by the extended links. Two isolation problems would still remain: removal of the hydrated catalyst, and isolation of any carboxylate/carboxylic acid cyclodextrin derivatives.

Having separated undesirable side-products from the capped cyclodextrins, a more difficult question of regioisomeric resolution remains. Many of the problems involved with previous work-up of capped cyclodextrin revolves around the separation and quantitation of A,C and A,D regioisomers. Since most previous capping studies have been directed at creating an intermediate for eventual multifunctionalization of the cyclodextrin's primary rim, separation has involved removal of the cap. Resolution by HPLC with reverse phase C_{18} is easily amenable to quantitation via UV-VIS interface; however, A,C and A,D regioisomers of rigidly-capped cyclodextrins are not separable by any known elution system.

The alternate technique involving conversion of a crude mixture of the regioisomers to their diamine derivatives, followed by silylation, separation and regeneration, is not directly applicable to our synthetic goals as it involves removal of the capping agent. We need a technique that can separate the fully capped cyclodextrins without effectively irreversible modification, and this has yet to be accomplished for A,C/A,D regioisomerism.

In the present study the use of anthraquinone as a capping agent avoids many of the problems mentioned. The rigid intramolecular reactive center distance enforces two related limitations: dicapping will not be efficient, even with the stoichiometric excess used in Table 5(#3,6), and a nearly exclusive A,D regioisomeric distribution should be expected. Whether or not this is of any consequence for the long-range photocatalytic goals is not clear; however, it does help make the extremely tedious separation and isolation procedure more manageable, owing to the fewer number of side-products to be expected. This in turn makes a systematic study of the effects of the reaction parameters of temperature, time, stoichiometry and concentration less critical to the immediate synthetic goals.

SPECTRAL ANALYSIS

After synthesis, isolation, and purification of our target molecule, what type of spectral evidence would be necessary in order to claim that we have a particular quinone-capped cyclodextrin? Certainly it would be imperative to establish the existence of the basic units: quinone, cyclodextrin, and the carboxylate or sulfonate links. Other types of associations between the basic components which might give similar spectral evidence would also have to be ruled out. A more subtle and demanding requirement involves distinguishing among various regioisomers.

Given the absence of standards for these novel compounds, we can make analogies with known rigidly-capped cyclodextrins, always considering that spectral behavior of a product is not necessarily a sum of its component parts. The spectra of modified cyclodextrins are of limited use for full characterization of products; the extreme difficulty involved in getting pure samples without destructive transformations guarantee that statements based on spectral data must be rooted in other inferences: the expected product from chosen reaction conditions, and the details of the work-up procedure.

(A) NUCLEAR MAGNETIC RESONANCE

(1) ^{1}H NMR. The stoichiometry of cap to cyclodextrin may be established by the ratio of the integrated areas of the anomeric cyclodextrin protons to the aromatic quinone protons; therefore, capped and dicapped cyclodextrins are distinguishable even under fairly low resolution. With this information, we must also be able to exclude possibilities of an included cap,or a cap on the secondary face.

Direct evidence of the former lies in the ^{1}H NMR: the C_3-H and C_5-H protons are directed towards the interior of the cavity, and their signals should show a significant upfield shift[91] when compared with those of the C_1-H, C_2-H and C_4-H protons, which are directed towards the exterior of the cavity. The penetration of the benzenoid rings of the quinone into the cyclodextrin would create anisotropic deshielding on the H-3 and H-5 protons. This effect may vary slightly for a benzoquinone derivative, which although not strictly benzenoid, possesses two ethylene units to interact with the interior protons.

For the quinones, the additional presence of the ring carbonyls on a possible included guest could introduce shift changes for interior protons that are in close proximity to the electronegative oxygens, depending on the degree of intrusion into the cavity. This latter parameter would be effected by the nature of the linking groups; with carboxylate or sulfonate anions, ^{1}H NMR in D_2O could be representative of a centrally situated guest, with ionic groups protruding out from the open ends of the cavity. This observation should reinforce care when interpreting these type of spectra: if done in D_2O, conclusions concerning the shift will reflect the preference of the guest for the hydrophobic environment of the cyclodextrin cavity. If done in pyridine-d_5, however, conclusions must take into account that an aromatic guest will not necessarily prefer the environment of the cavity to the non-aqueous conditions of the solvent. For elimination of the possibility of a quinone inclusion complex, it may be sufficient to point out that no recorded case exists of any such complex surviving the work-up conditions used for these capped cyclodextrins.

For elimination of the possibility of capping on the secondary face, ^{1}H NMR integration area ratios of primary to secondary hydroxyl protons are not useful. The relative values of 5:14 for the primary face monocap and 7:12 for the secondary face monocap reduce to 0.38 and 0.58, respectively; however, the interaction of $C_{2,3,6}$-OH protons with quinone carbonyls could cause shifting that would make quantitative approximations unreliable. Here again, the identity of the NMR solvent gives us some clues: even DMSO will not break the characteristically strong hydrogen bonding of the secondary hydroxyl protons, which are consequently more resistant to the hydrogen-deuterium exchanges in D_2O. In the latter solvent, secondary and primary hydroxyl protons are often not distinguishable.

It is possible that bidentate and monodentate dicapped cyclodextrins may be qualitatively distinguishable by the nature of the aromatic signals: the freely spinning monodendate caps should exhibit sharp resonances and splitting, rather than those of aromatic protons that are motionally hindered. How much freedom of movement a rigid cap on a cyclodextrin will have, and whether qualitative effects on the spectra would be useful is not clear. The primary to secondary hydroxyl proton ratio of 5:14 for the monodentate dicapped is the same as that of the primary face monocap, but very different from the 3:14 ratio for the bidentate dicapped. The two types of dicaps may have very different R_f's on silica, therefore, the separation procedure should supplement any inferences based on spectral data. Assuming we have enforced hydrolysis of the free links of any carboxylic or sulfonic acid chlorides, we still should not expect to be able to consistently see an aromatic carboxylic acid proton in the spectra, and therefore could not reliably distinguish monodentate and bidendate caps on this basis.

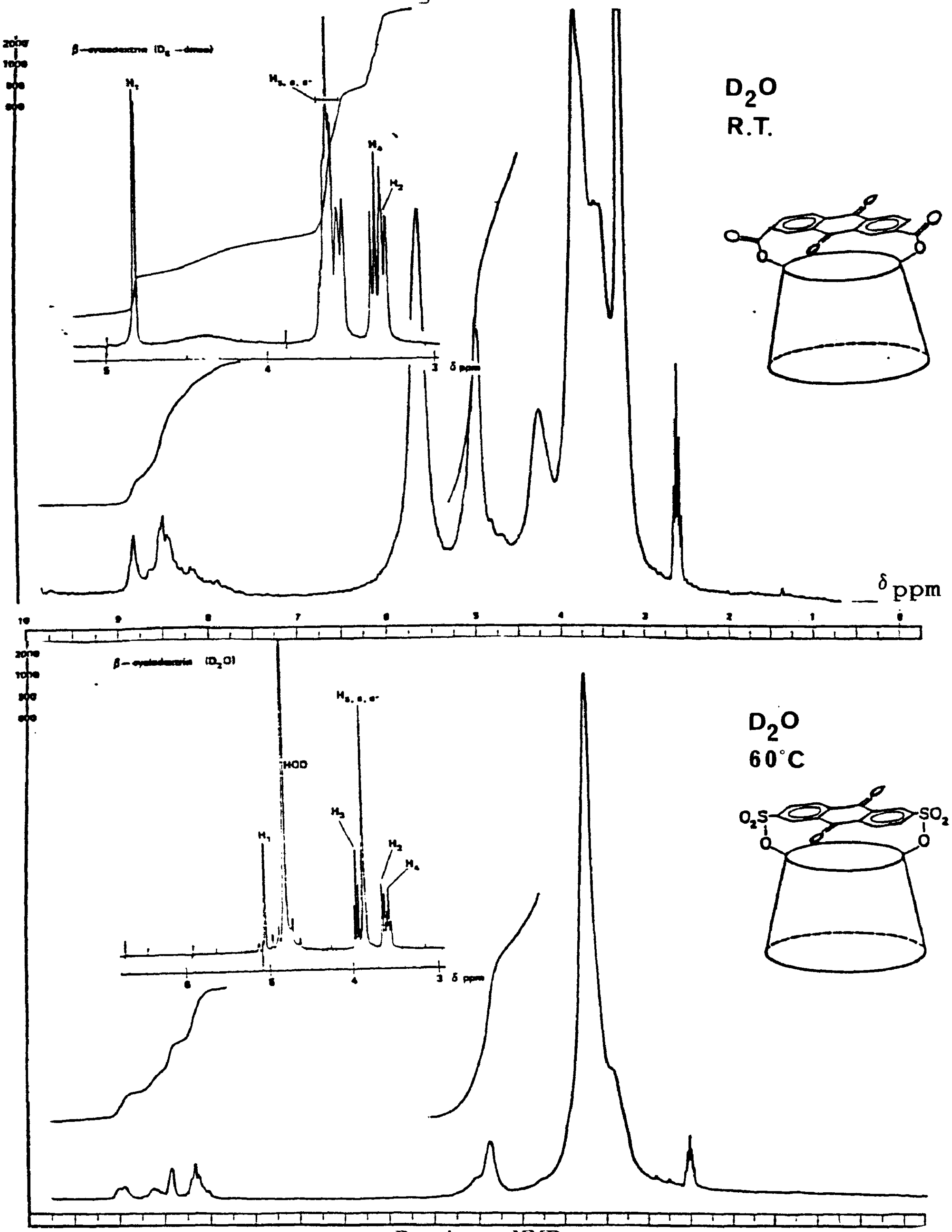
Several other interesting possibilities exist: monodentate tricaps, a combination of bidentate monocap and either one or two monodentate caps, and perhaps even an included cap in combination with monodendate or bidentate caps. This last possibility reinforces the importance of anhydrous reaction conditions: the absence of hydrolyzed links favor bidentate attachments and the build-up of polymeric material(Figure 27), the latter being most easily separated from the desired target molecule.

Figure 29 helps focus the difficulties in using low field NMR for interpretation of proton resonances: in the disulfonyl cap spectra, only the anomeric C_1-H resonance at $\delta = 4.8$ shows separately from the others at $\delta = 4.3$-2.3, centered at 3.8; in the dicarbonyl cap spectra, a possible C_6-OH peak exists at $\delta = 4.3$, but the obscured baseline does not allow a comparison of integration area with the possible $C_{2,3}$-OH peak showing at $\delta = 5.7$.

In the cyclodextrin treated with anthraquinone 2,7-dicarboxylic acid chloride, it is not clear what effect decreased rigidity in the capped structure would have on chemical shifts of other protons: the 2,7- isomers of both anthraquinone derivatives would arguably have more freedom of movement, and their ring carbonyls would be in a better position to deshield protons on the primary rim or cavity interior.

This last observation is is not clarified by the ^{1}H NMR(DMSO-d6) for non-anomeric proton shifts by the derivatives in Figure 10: for 10a, $\delta = 2.8$-4.7(m, 61H); for

Figure 29



Proton NMR

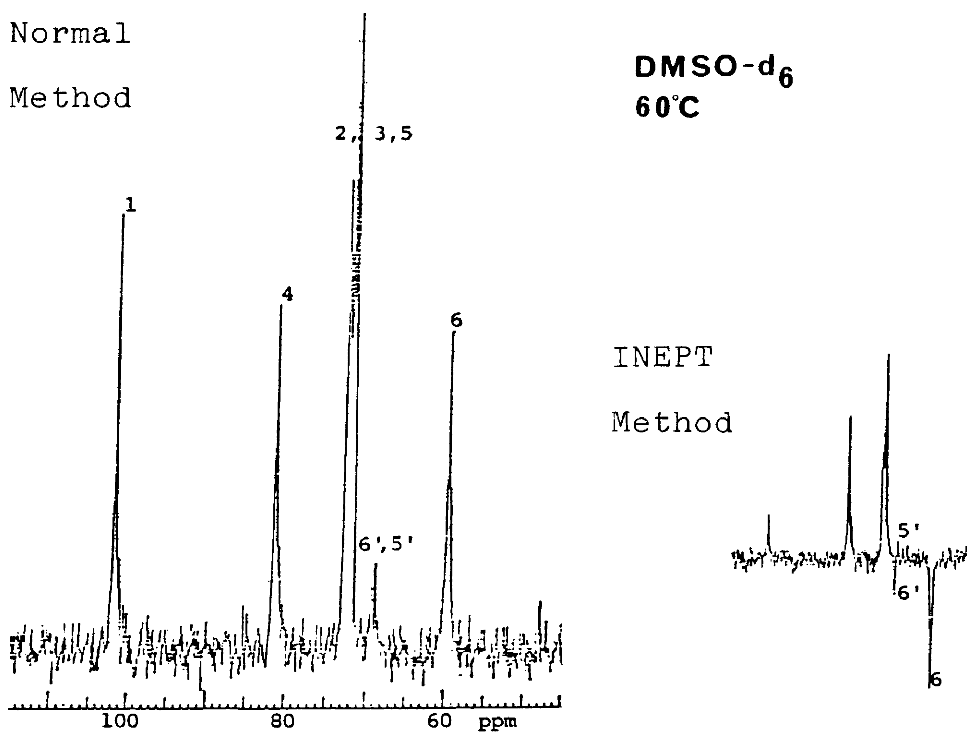
10b, δ= 3.3(42H), 4.3, 5.53(19H); for 10c, δ= 3.3(42H), 4.4, 5.7(19H). The spectra for 10a reflects the greatest degree of cap intrusion into the cyclodextrin cavity; the spectra from 10b and 10c simply allow us to place the hydroxyl protons if they show up separately. Comparison and contrast with standard spectra of unmodified cyclodextrin in D_2O and DMSO(Figure 29 inset) reinforce that ^{1}H NMR is mainly useful for establishing the stoichiometric ratio of cap to cyclodextrin.

(2) ^{13}C NMR. Given the limited information available from the ^{1}H NMR spectra, it is fortunate that ^{13}C NMR can show more precise information about the quinone cap attachment. For the sulfonyl group substitution, Breslow found that the resonance from the substituted carbon will be shifted downfield, and those for the neighboring carbons on either side will be shifted upfield.[92] In order to determine the tosylated positions of cyclodextrins, the spectra for monotosyl derivatives have been examined[93] to ascertain whether peaks were due to the methylene carbon at the C-6 position, or the methine carbons at the C-2 or C-3 position. The use of the INEPT method allowed them to distinguish between shifts arising from substitution on the primary or secondary face. Figure 30 shows two spectral techniques applied to the products arising from the treatment of

β-cyclodextrin with 1.8 equivalents of tosyl chloride at room temperature, for one hour in an aqueous alkaline solution.

When the carbon attached to the point of substitution is bonded to two hydrogens, as in the case of primary face capping, the C-6' signal is directed down; all other cyclodextrin carbons are bonded to a single hydrogen, and their respective C' shifts will be directed upwards. In the tosylation study, this is what allowed the investigators to tell on which face the modification had occurred, and in the case of secondary face tosylation, which carbon had been subject to hydroxyl modification.

Figure 30. ^{13}C NMR in 1^{o} and 2^{o} Hydroxyl Modification



Applied to capping reactions, the INEPT method would allow us to add an additional piece of information to the cyclodextrin/cap stoichiometric ratio gained from ^{1}H NMR. Owing to the inability of the NMR used in this study to offer this capability, it becomes mandatory to stick to the known reaction parameters used by Tabushi in Table 3: no examples of secondary face capping are known to have occurred under these conditions.

Having accepted the probability of quinone capping on the primary face, a more difficult question of regiochemistry still remains. As mentioned in **SEPARATION AND PURIFICATION**(pg. 67) the bis((p-tert-butylphenyl) sulfenyl derivatives of cyclodextrins may be separated by HPLC. For a mixture of rigidly capped cyclodextrins, the respective retention times for A,B, A,D, and A,C-bis(p-tert-butylsulfenyl) cyclodextrins were 11.6(Band 1), 13.0(Band 2) and 15.2(Band 3)minutes on a 900 p.s.i. carbohydrate column with elution by 3.5:1 CH_3CN/H_2O at 2.0 ml/minute.

How were the matching of R_t and regiochemistry made? In a study with compound (a) from Figure 10 A,B functionalization can be distinguished from other isomerism by the effect of a remote substituent on ring A on the high field ^{13}C NMR chemical shift on ring B.[93] The ^{13}C chemical shifts of C-1', C4' and C-6' on the glucose ring bearing the substituent X(A) are strongly affected by a substituent X(B) on the adjacent ring, while the C-1,4,6 ^{13}C shifts on the other rings are only slightly affected by X(A). Consequently, a clear chemical shift difference of 0.54 ppm between the C-4' on ring A and B can be used to distinguish between A,B and either A,C or A,D regioisomers; the latter two exhibit practically nonexistent splitting of the C-4' absorption.

A,B regioisomers were therefore identified with Band 1; the assignment of structure was supported by MS on the Taka-amylase-catalyzed hydrolysis products of the isolated bands. The A,C regioisomers exhibit ^{13}C NMR spectra which are very similar to the A,D isomers; therefore, another approach was needed to match A,C and A,D isomers with either Band 2 or 3.

Compounds (b) and (c) from Figure 10 were used in two-fold excess(Table 3, #2,7) in studies designed to elicit dicapping. When bulk mixtures from each reaction were converted to their bis(sulfide) derivatives, only the product from the 10b treatment showed a component with a distinctly different R_t, which was thereby identified as the tetrasubstituted dicap derivative. It is implied, although not stated explicitly by Tabushi, that this was used to develop an internal standard to reference Bands 2 and 3, the latter now being matched with compound 10b. Based on the large intramolecular reactive center distance of 10c, which should preclude A,C linkage and subsequent dicapping with a stoichiometric excess, it was inferred that Band 2 must represent A,D regioisomerism.

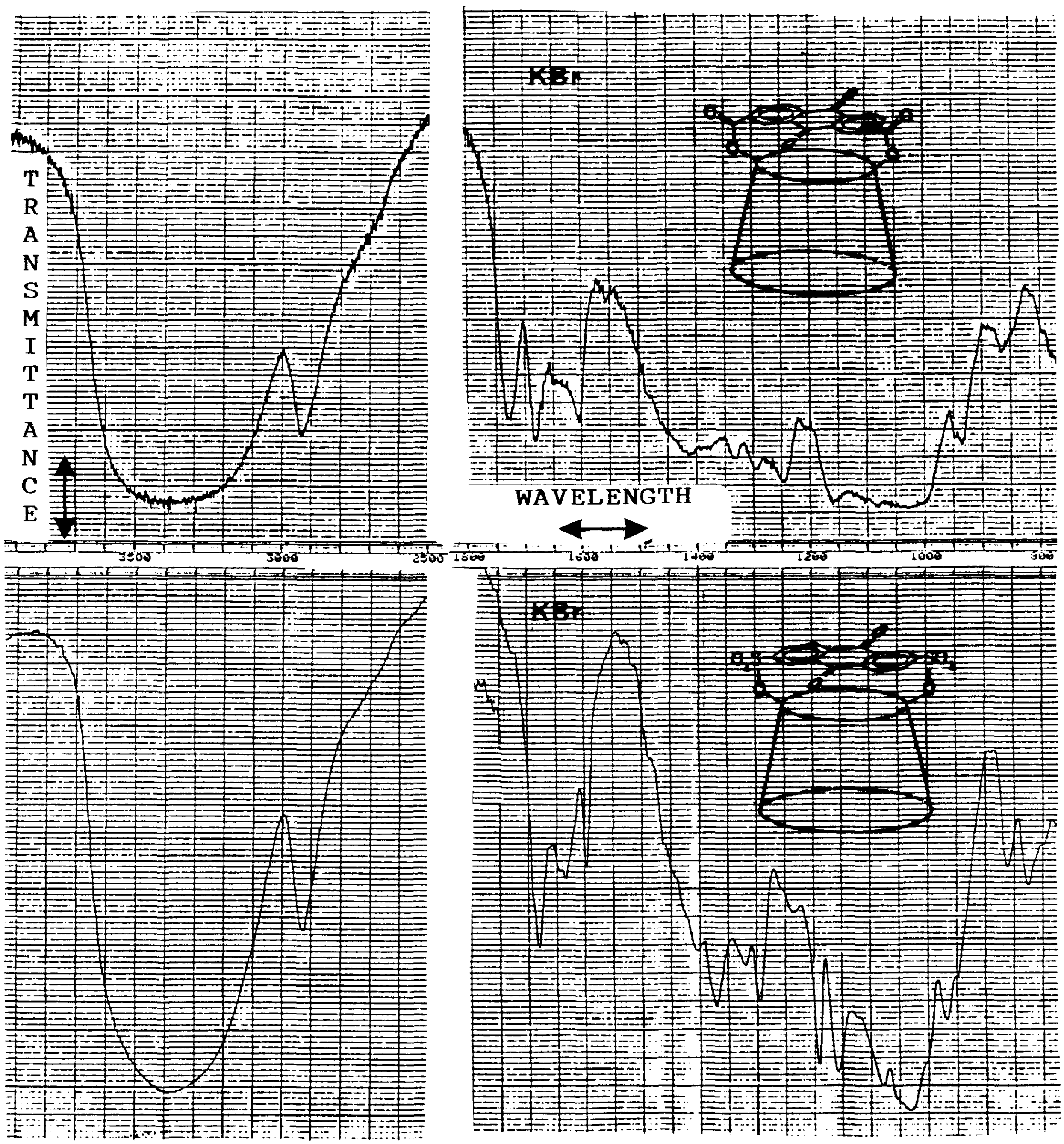
It is this type of argument, using the details of the simple capping model and chosen work-up procedure to deduce expected products from chosen reaction conditions, that allows the spectral data of modified cyclodextrins to be useful. Since rigidly capped A,C and A,D cyclodextrins cannot be separated by any known chromatographic system, their conversion to disubstituted cyclodextrins along previously mentioned schemes, followed by HPLC is necessary for isomeric purification. Consequently, a synthetically useful way to pure A,C or A,D capped cyclodextrins is not clear. Without an available technology to separate capped cyclodextrin isomers, the inability to distinguish between similar ^{13}C NMR is not critical.

The low-field NMR spectra used in the present study was useless for making any definitive statements from ^{13}C. By using an anthraquinone reagent, however, selective A,D capping is enforced by the large intramolecular reactive center distance, and some of the subtler regioisomeric problems are side-stepped.

(B) INFRARED SPECTROSCOPY

IR is of limited value for detailed characterization, although it is useful for establishing some of the basic units which we must see if the compound in question is indeed a quinone-capped cyclodextrin. Figure 31 mainly

Figure 31



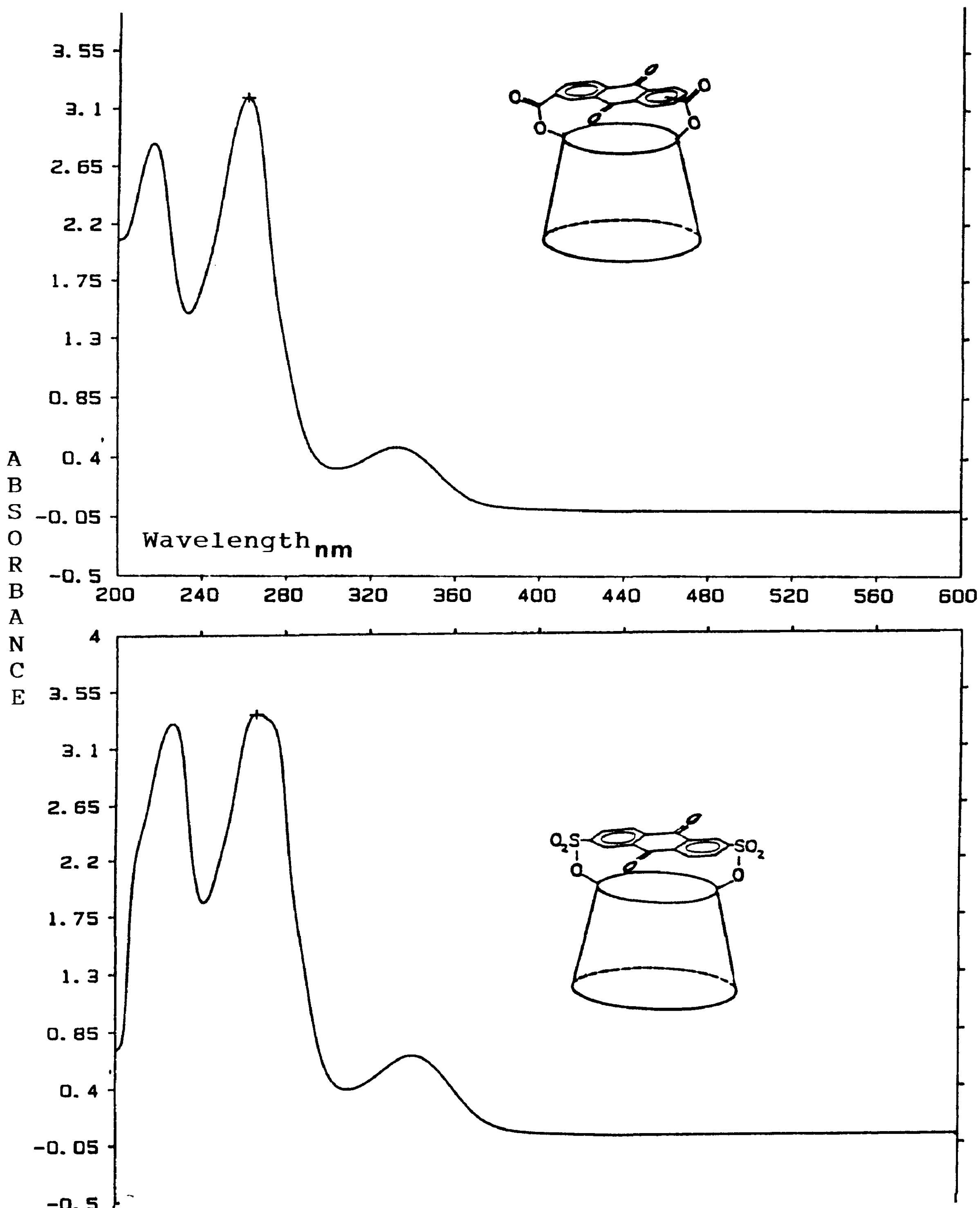
Infrared Spectroscopy

serves to establish the presence of linking groups from the modified quinones: the asymmetric carbonyl stretching vibration at 1720 cm^{-1}; and the asymmetric and symmetric sulfonyl stretches at 1370 and 1160 cm^{-1}, respectively. The nuclear carbonyl quinone peak at 1680 cm^{-1} can be clearly seen for each derivative. The broad, rolling band in the hydroxyl area, 3500-3300 cm^{-1}, is characteristic of cyclodextrin. Nothing else can be claimed from the spectra.

(C) ULTRAVIOLET SPECTROSCOPY

Assuming the applicability of the Beer-Lambert relationship, the presence of a dicapped cyclodextrin, or of an excess quantity of starting quinone should result in enhanced absorption in the UV region, where cyclodextrin is inactive. Figure 32 shows the strongly allowed quinonoid π-π* transition at 258-261nm and the allowed benzenoid π-π* transition at 333-334nm. The latter should be the most useful support for a monocapped structure: it is less environment dependent than the former, and more reflective of quinone substitutions, which must take place on the benzenoid rings. For anthraquinone in methanol, $\lambda_{max}(\log \epsilon) =$ 325nm(4.02); for 2-anthraquinonesulfonic acid in water this shifts to 330nm(3.72).[94] For the proposed anthraquinone-2,6-disulfonyl capped cyclodextrin, the absorbance at 334nm was 0.653, which for an assumed monocap concentration of 1.27×10^{-4}M, gives $\log \epsilon = 3.71$. Similar calculations give agreement for mono-dicarboxylate capped cyclodextrin.

Figure 32



Ultraviolet Spectroscopy

EXPERIMENTAL

(A) INSTRUMENTS, APPARATUS, MATERIALS.

Commercially available cyclodextrin(Aldrich) was used after vacuum drying(0.05mm) at 110^{o}C for 12-16 hrs with a liquid N_2 trap; the pyridine was purified by refluxing over KOH for 12 hrs, then distilled just prior to use. ^{1}H NMR and ^{13}C NMR were recorded on a Varian FT-80A. IR spectra were obtained using a Perkins-Elmer 983; electronic absorption spectra were measured on a Beckman DU-70. TLC was carried out on 0.25 mm(60F-254) precoated silica plates(Baker); spot detection was done with UV and staining with 4-hydroxy-3-methoxybenzaldehyde(Fisher). Column chromatography was done with silica (60-200)[Baker], and alumina(neutral, 80-200)[Fisher]; cation exchange was accomplished with Dowex 50 W-X12(200-400 Na/H+)[Baker], anion exchange with AG1-X8(200-400 Cl)[BioRad]; reverse phase with bonded octadecylsilane(40-μm)[Baker]. Melting points were uncorrected, taken on a Hoover(Thomas) capillary m.p. apparatus. Autoclave procedures were done in a 300 ml Magne-Drive II(Autoclave Engineers).

(B) DICARBOXYLIC ACID CHLORIDES

(1) Anthraquinones

4-methyl-1,2,3,6-tetrahydrophthalic anhydride. The Diels-Alder conditions used here were adapted from a procedure for the preparation of the 3-methyl isomer:[95] gentle reflux of 75.0 g of maleic anhydride and 52 g of isoprene in 250 ml of benzene with a catalytic amount of picric acid. The explosive nature of the dry catalyst precludes an accurate weighing; therefore, in order to determine the optimal amount, several runs were made with a varying, yet consistently measured wet weight of picric acid, while keeping the solvent volume and reactant weight constant.(Table 2) With 0.69 g wet weight of picric acid, evaporation of excess isoprene and solvent under reduced pressure gave a yellow liquid which solidified as it cooled. Recrystallization from benzene/pet-ether with decolorizing carbon gave 98.04 g(77%) of colorless prisms; m.p. 62-64^{o}C (Lit. 63^{o}C),[70] with an IR(KBr) compatible with standard Sadtler spectra #6305.

4-methylphthalic anhydride. Aromatization of the addition product was completed by modification of a procedure used for preparation of 3-methylphthalic anhydride:[96] dropwise addition, over a period of 1.5-2.0 hrs, of 124 g of bromine in 110 ml of glacial acetic acid to a 100°C solution of 50 g of 4-methyl-1,2,3,6-tetrahydrophthalic anhydride in glacial acetic acid. After 16 hrs reflux, the solution was concentrated by evaporation under reduced pressure, then the residue heated for 5.5-7.0 hrs at 220-230°C. Yield and convenience of operation improved with the use of a water-filled gas trap to catch evolving HBr. Distillation at 0.05 mm gave a colorless liquid coming off at 130°C, with immediate solidification. A recrystallization from benzene/pet-ether with 20-30% excess of the latter gave varying yields of 55-73%, the upper limits associated with the strictest temperature control during pyrolysis. Colorless prisms; m.p. 94-96°C (Lit. 93°C);[97] IR consistent with aromatization of Sadtler spectra #6305.

Preparation of 3,4'(3')-dimethylbenzophenone-6-carboxylic acid. The procedure follows the method and stoichiometry for the preparation of p-toluyl-o-benzoic acid:[98] condensation of 32.5 g of 4-methylphthalic anhydride and 120 g of toluene with 99.99% $AlCl_3$(Aldrich) yielded 22.5 g(44%) of white powder; m.p. 140-142°C (Lit. 164°C);[68] IR(KBr), 3500-3200, 1650 and 1680 cm^{-1}.

2,6 and 2,7-dimethyl anthraquinones. 25 g of the acid mixture was treated with 248 g H_2SO_4(15% SO_3) at

125-130°C for one hour. Work-up followed the procedure[99] for the ring-closure product with p-toluyl-o-benzoic acid. The resulting 21.3 g(82%) of tan product was sublimed to give 19.6 g(92%) of light yellow powder, for a total yield of 75%; m.p. 195-210°C. Three recrystallizations from glacial acetic acid gave needles, m.p. 238°C (Lit. 242°C);[68] three recrystallizations from ethanol gave feathery needles, m.p. 159-162°C(Lit. 170°C).[67]

Oxidation of dimethyl anthraquinones. For a modification of the procedure for 2,3 dimethyl naphthalene,[100] a 300 ml Magne-Dash equipped autoclave was charged with 6.5 g of dimethyl anthraquinone and 40.0 g of sodium dichromate dihydrate in 65 ml of water. The temperature was maintained at 195-200°C for 20 hr with stirring at 60 c.p.m.

After cooling to 70°C, the pressure is released and the autoclave emptied and rinsed with 5x40 ml portions of hot water. The green, hydrated chromium oxide was separated on a large Buchner funnel, then washed with small portions of warm water until the filtrate was clear, or failed to precipitate out material upon acidification with HCl. The combined aqueous fractions are acidified with a minimal amount of 6N HCl, and after cooling in an ice bath, the precipitated solid is removed by suction filtration, and washed with cold water until the filtrate is clear. After standing in air for a few hours, the solid is dried overnight under a vacuum. Starting material may be reclaimed from the chromium oxide solids by extraction with toluene. After work-up: 62% yield at 60% conversion to the diacid quinone; m.p. greater than 290°C; IR(KBr), 1660, 1690, 3500-3300, 3100-2800 cm^{-1}.

Anthraquinone-2,6-dicarboxylic acid chloride. The diacid quinone is treated with three equivalents of PCl_5 at 110°C for 4-5 hours. The reaction mixture is cooled, then quenched slowly with small portions of ice until the evolution of gas abates. The solids are suction filtered, then washed with cold water until the filtrate is clear. Vacuum drying of the residue overnight, followed by sublimation gave 77% of yellow powder; m.p. 197-199°C (Lit. 198°C).[65]

(2)Benzoquinones

2,5-dicarbomethoxy-1,4-cyclohexanedione. In the modification of a procedure for synthesis of 1,4-cyclohexanedione,[101] sodium methoxide was prepared in situ by dissolving 5.0 g of metallic Na in 75 ml of methanol under a nitrogen atmosphere, followed by 2-3 hr of reflux. 14.6 g of dimethyl succinate is added in one portion, with reflux continuing for another 24 hrs. The ethanol is then removed by evaporation under reduced pressure, and the residue treated with 100 ml of 2N sulfuric acid, with vigorous stirring for 2-3 hrs. The solid is removed by suction filtration and washed several times with small portions of water. The clay-like material is dissolved in 75 ml of boiling ethyl acetate, gravity filtered, then left overnight for recrystallization. The product comes out as the strongly enolised cyclohexa-1,4-diene-2,5-diol-1,4-dimethyl ester: m.p. 160-164°C; IR(KBr), 1660(broad shoulder at 1630), 3080(broad) and 3270 cm^{-1}(sharp); ^1H NMR($CDCl_3$), singlets at 3.79(6H) and 3.15(4H); yield: 5.9 g(56%).

2,5-dichloro-3,6-dicarbomethoxybenzoquinone. 1.0 g of the dimethyl ester in 15 ml of chlorine-saturated glacial acetic acid was refluxed for two hours with continuous bubbling of gaseous chlorine through the solution. The use of an acetonitrile:liquid nitrogen slurry(-41°C) in a condenser placed over the reaction vessel established a chlorine reflux that circumvented the literature's[38] use of a concentrated solution of 1g Cl/ml acetic acid. Care must be taken to establish a moderate rate of cycling that does not lead to freezing of the reaction solution by re-precipitating liquid chlorine(-34°C). After the gas flow has been stopped, temperature is maintained at 65°C for 16 hrs. Upon cooling, the precipitate may be filtered, air dried, then sublimated to give 0.80 g(62%) of yellow crystals; m.p. 242-243°C(Lit. 240°C);[38] IR(nujol), 1744 and 1680 cm^{-1}; ^{1}H NMR($CDCl_3$), singlet at δ= 6.02. The known method gave a mixture including the analogous hydroquinone, lowering the yield(51%) and introducing extra purification steps(recrystallization and chromatographic separation) and the need to interconvert to the desired quinone or hydroquinone.

Attempted ester hydrolysis of 2,5-dichloro-3,6-dicarbomethoxy-benzoquinone

Acidic catalysis 0.25 g of the chlorinated quinone in 30 ml dioxane treated with: (I) 30 ml of 6M HCl at room temperature overnight, (II) 30 ml of 1.5M HCl at reflux for one hour, (III) 45 ml of 1.6M HCl at reflux for six hours. From work-up of (I), 0.15 g of tan product, m.p. 170-174°C; IR(nujol), 1700 cm^{-1} with broadening at 3400-3200 cm^{-1}; ^{1}H NMR singlets at 4.03(3H) and 9.26(1H). No resolution on silica with methylene chloride; after sublimation, 0.08 g, m.p. 178-182°C. From work-up of (II), 0.09 g, m.p. 172-174°C; similar spectral data as (I). From work-up of (III), 0.07 g, m.p. 173-174°C; also with similar spectral data.

Nucleophilic displacement 1.65 g of LiI in 45 ml dry pyridine with 0.25 g of chlorinated quinone, under nitrogen, in four trials: at room temperature for both an hour and overnight; reflux for both an hour and overnight. All reaction conditions led to miniscule amounts of unidentifiable products.

Direct cleavage with phosphorous pentachloride 0.25 g of chlorinated quinone in 15 ml dry methylene chloride was added dropwise to 1.0 g of PCl_5 which was stirring in 10 ml of dry dichloromethane at $0^{o}C$ under nitrogen. After 1.5 hrs, the temperature was raised to $45^{o}C$ with application of light aspirator pressure for 30 minutes. Sublimation of the residue led to recovery of 0.12 g of starting material.

Basic catalysis 0.20 g of chlorinated quinone was dissolved in minimal volume of THF, about 10 ml, then treated with 5 equivalents of KOH in 3 ml of water at room temperature overnight. Work-up led to the recovery of 0.15 g of starting material.

Attempted oxidation of 1,4-dicarbomethoxy-cyclohexa-1,4-diene-2,5-diol

2,3-dichloro-5,6-dicyano-benzoquinone(DDQ) 0.15 g of the dimethyl ester in 10 ml of dioxane was treated with 0.35 g of DDQ at: (I) room temperature with stirring overnight;

(II) reflux temperature overnight. From (I), TLC on silica with methylene chloride could not distinguish between the reaction mixture and starting materials. From (II), removal of solvent under aspirator pressure, then treatment of the residue with methylene chloride was followed by gravity filtration of the suspended solids. The brownish filtrate was run through a short silica column and flushed with methylene chloride. Evaporation of the eluent under reduced pressure led to a miniscule deposit of bright yellow powder; IR(KBr) showed splitting of broad carbonyl at 1660 cm^{-1}.

Jones reagent A standard solution of Jones reagent was prepared by addition of 5.47 g CrO_3 to 10 ml of distilled water with 4.64 ml of concentrated sulfuric acid. 0.68 g of the enolised dimethyl ester was dissolved in a minimal amount of distilled acetone, then titrated with the Jones reagent until orange endpoint persisted for more than 15 minutes. Decanting, followed by combination of liquid with acetone washings of the green chromium crystals yielded an orange liquor. Excess chromic acid was neutralized by addition of isopropanol until the orange color disappeared, then complete neutralization with sodium bicarbonate. Gravity filtration of the solids, followed by evaporation of solvent from the liquor left a residue that could either be re-dissolved in methylene chloride or extracted with a NaCl:water/ether solvent system. In both cases the organic layer could be evaporated under reduced pressure, giving a return of starting materials with no identifiable quinone.

Manganese dioxide The general procedure for oxidation of the hydroaromatic cis-dienol calls for a 15-fold excess of MnO_2 in an inert solvent under nitrogen atmosphere, with stirring. Conditions used here: (I) 1.3 g of the dimethyl ester with 7.6 g of activated MnO_2 in 40 ml of chloroform for one day at room temperature; (II) 1.0 g of the dimethyl ester with 5.3 g of the oxidant in 110 ml of benzene for one week at room temperature; (III) 0.71 of the dimethyl ester with 5.6 g of the oxidant at reflux in benzene, with azeotropic distillation by Dean-Stark trap for 16 hrs. All three treatments gave only the return of starting materials.

2,5-dihydroxy-p-benzenediacetic acid.[60] Three solutions are prepared: (I) 30 ml of ethyl cyanoacetate and 100 ml of 95% ethanol; (II) 54 g of p-benzoquinone in 500 ml of ethanol at 40°C, with 56 g of ethyl cyanoacetate added after dissolution of the quinone; (III) 100 ml of conc. ammonium hydroxide in 150 ml of water. After this preparation, 25 ml of conc. ammonium hydroxide is added to (I), which is stirring in a 3-l. round-bottom, three-necked flask situated in a bath with a constant flow of cool water through it. (II) and (III) are added dropwise so that there is simultaneous delivery to the reaction vessel over a period of 45 minutes. Stirring continues for another 15 minutes, followed by standing for one hour. Suction filtration of the solid followed by washing with ethanol gave 46 g(55%; Lit. 43-49%) of diethyl-α,α'-dicyano-2,5-dihydroxy-p-benzenediacetic acid. 36 g of this adduct was refluxed in a solution of 210 ml of conc. HCl in 190 ml of water for 20 hrs. Decolorizing with 6 g of Norit A, followed by rapid suction filtration while hot gave 16 g of a pale-white powder upon cooling to 20°C; m.p. 235-237°C(Lit. 233°C); yield: 62%(Lit. 61%).

3,6-diketo-1,4-cyclohexadiene-1,4-diacetic acid.[59]

2.0 g of the hydroquinone was added to 225 ml of water, cooled to 15°C, then treated with 0.8 ml of conc. sulfuric acid. 1.3 g of potassium dichromate was dissolved in a minimal volume of water, then added dropwise to the acidic solution, with temperature maintenance and stirring. 1.6 g(78%) of yellow crystals separate out; m.p. 186-188°C(Lit. 185°C) after suction filtration and drying.

Benzoquinone-2,5-diacetic acid chloride

Thionyl chloride $SOCl_2$ was purified by distillation from a 10%(v:v) solution with triethyl-phosphite.

Functional group transformation attempted: (I) without catalyst by (a) 0.25 g of the diacid in 50 ml of thionyl chloride, refluxing for 2.5 hrs; (b) 0.20 g of diacid in 50 ml of thionyl chloride, refluxing overnight; (II) with 0.3 ml of pyridine catalyst in 5 ml of dry ether cooled to -5^{o}C with 0.50 g of suspended diacid. With temperature control at 0^{o}C, 0.95 ml of thionyl chloride is added dropwise, then left standing for one hour. After evaporation of solvents under aspirator pressure, the reddish-brown precipitate was dissolved in dry acetone, leaving a black precipitate. IR of the acetone residue(neat) showed a shift of the carbonyl peaks to 1810 and 1775 cm^{-1}, with a strong absorption at 720 cm^{-1}. ^{1}H NMR showed distinct absence of methylene protons; little else that was interpretable. TLC's on silica with methylene chloride and varying ratios of either pentane or acetonitrile did not lead to a satisfactory resolution.

<u>Phosphorous pentachloride</u> 0.37 g of purified diacetic acid quinone(recrystallization from 95% ethanol) in 5 ml of dry methylene chloride at 0^{o}C, followed by dropwise addition of 0.70 g of PCl_5 in 25 ml of dry methylene chloride; left stirring overnight at room temperature under nitrogen. TLC's on silica with 9:1 methylene chloride:acetonitrile indicated absence of product. Evaporation of solvents and excess PCl_5 under reduced

pressure required heating to 90°C, and elicited a gradual darkening of the residue. IR of pot(neat), 1820 and 730 cm^{-1}(strong); TLC on silica with methylene chloride, R_f= 0.8. Residue run on a short silica column with methylene chloride eluent, evaporation under reduced pressure left a pale tan-yellow product. IR(KBr), 1820 and 730 cm^{-1}; m.p. 130-200°C; ^1H NMR($CDCl_3$), δ= 3.75 and 6.90, (acetone-d_6), 4.00 and 7.20. Introduction of water led to a decreased peak height at 3.85 and 7.35: integrations not useful owing to overlapping resonances. TLC's of $CDCl_3$ and acetone-d_6 fractions gave identical R_f's; stained bright yellow with vanillin. Sample continued to darken with exposure to air, giving off a pungent, chlorine-like odor.

<u>Phosphorous pentachloride(modified)</u> 25 ml of dry benzene with 2.88 g of PCl_5 at 0°C, addition of 1.55 g of diacid quinone with stirring, then gradual warming until reflux achieved. After 5 minutes the heating was discontinued, and after the vigorous evolution of HCl abated, the excess solvent was evaporated under reduced pressure. Just prior to dryness, the reaction was quenched with a small amount of ice, evaporated, then treated with enough methylene chloride to facilitate dissolution of the majority of the residue. The liquor was decanted, the solvent evaporated, and the resulting bright yellow solid

was dried under a vacuum until used for the capping reaction. IR(KBr), 1810 and 730 cm^{-1}; decomposed quickly in air.

(3) Naphthoquinones

Dimethyl-naphthoquinone

Friedel-Crafts method Added 8.0 ml of citraconic anhydride to an ice-bath cooled flask stirring with 90 ml of toluene, and fitted with a calcium sulfate drying tube. 22.4 g of $AlCl_3$ was added in one portion, the ice bath removed after 15 minutes and replaced by an oil bath for gradual heating to 90°C. After 2.5 hrs at this temperature, another equivalent of $AlCl_3$(11.1 g) was added for overnight stirring. After gradual cooling of the reaction mixture to ice-bath temperature, the reaction was quenched with ice and HCl, followed by extraction with 2x100 ml portions of ether. The organic fraction was washed with water, followed by 3x75 ml portions of saturated $NaHCO_3$/water. The aqueous layer was titrated with HCl, while the organic layer was dried and evaporated. TLC's of both the aqueous and organic fractions against starting materials on silica with methylene chloride eluent indicated two new species: R_f= 0.85 and 0.19, common to both the organic and aqueous samples, although with a much higher concentration of each in the organic, particularly the faster moving component. The evaporation of the organic layer left a dark maroon gum; column chromatography was attempted on silica with a gradient elution of 1:1, 2:1 and 4:1 CH_2Cl_2:hexane. Two distinct bands separated: IR(nujol), first band: 3600-3100, 1630 cm^{-1}, second band: 1690 cm^{-1}; ^1H NMR($CDCl_3$) shows uncharacterizable mixture, δ = (m 7.5-7.0), (s 2.4, 2.3). Same gradient elution tried with alumina, without result; changing solvent system to methylene chloride:acetonitrile elicited other bands, also uncharacterizable. Attempted sublimation of solid led to decomposition at 60°C.

Diels-Alder method 15 g of toluquinone and 22 ml of isoprene in 50 ml of methanol at 110°C in an autoclave for one hour; cooling, pressure release, methanol washings and collection of fractions left 16.4 g of product after solvent evaporation. TLC on silica with methylene chloride eluent indicated a mixture of products with R_f's of 0.73 and 0.28. Approximately 28% of the crude mixture was insoluble in benzene at room temperature; assuming a mixture of naphthohydroquinone and tetrahydronaphthoquinone gives a yield of 74% at 79% conversion, based on the amount of toluquinone recovered by fractional sublimation.

Manganese dioxide aromatization The major product from the Diels-Alder reaction (12.8 g) that was benzene-soluble was dissolved in a minimal amount, then treated with a 15-fold excess of MnO_2 under nitrogen at reflux for four hours; yield: 7.41 g(57%) of a dull yellow product. Sublimation gave 95% bright yellow powder; m.p. 105-120^o; ^{1}H NMR($CDCl_3$), δ=(s 2.2, 2.5), (m 7.5-8.1).

Attempted oxidation of dimethyl-naphthoquinone. 4.1 g of the dimethyl-naphthoquinone mixture was heated at 145-150^{o}C in an autoclave charged with 20.5 g of sodium dichromate dihydrate in 75-80 ml of water. After 20 hrs, standard work-up of the autoclave contents gave a maroon powder; IR(KBr), 3600-3300, 1710, 1670 cm^{-1}; ^{1}H NMR($CDCl_3$) indicated paramagnetic material; m.p. greater than 270^{o}C. TLC's on silica with methylene chloride indicated a fast, streaking spot with considerable baseline contamination; elution on a short column gave a lighter colored product; ^{1}H NMR still paramagnetic with some resonance in the methyl proton region.

(C) DISULFONIC ACID CHLORIDES

(1) Anthraquinones

Anthraquinone-2,6-disulfonyl chloride. Two general methods may be used, yields for both over several runs ranged from 36-47%.

Method I Anthraquinone-2,6-disulfonic acid disodium salt is treated with 3.9 equivalents of PCL_5 at 100-110^oC for 5-7 hrs under a calcium chloride drying tube. Quenching with ice is followed by suction filtration and washing with water until the filtrate is clear. The crude product is a yellow powder, 92-95% of starting material by weight. The diacid chloride may be partitioned off by boiling in methylene chloride; however, TLC's on silica with methylene chloride reveal fluorescent spot at solvent line, and another at R_f= 0.92, contrasted with the diacid chloride at 0.79(averages of several spottings). The methylene-soluble fraction may be sublimated after evaporation of the solvent: the faster spots come off at 130-160^oC; the diacid chloride, very slowly at 220^oC.

Method (II) In a modification of a procedure for 1,5-naphthalene disulfonyl chloride,[102] the disodium salt is dried under a vacuum at 100^oC for 48 hrs, then treated with 2.5 equivalents of PCl_5 under a calcium chloride drying tube for one hour at 110^oC. The $POCl_3$ and excess PCl_5 is removed under aspirator pressure, and the resulting dry cake is added to a 3:1 chloroform:water mix, then heated to boiling until nearly all the solid dissolves. The layers are separated while hot, the organic layer gravity filtered and allowed to evaporate to 1/4 volume for recrystallization.

Anthraquinone-1,5-disulfonyl chloride. Method (II) is most applicable, as the disodium salt exists as a hydrate of unknown association number.

(2) Benzoquinone

Benzoquinone-2,5-disulfonyl chloride

<u>2,5-dihydroxy-1,4-benzenedisulfonic acid</u> 5.0 g of 2,5-dihydroxy-1,4-disulfonic acid dipotassium salt was dissolved in 200 ml of water and run through a 50 g acidic cation exchange column, flushed with water until eluent neutral. IR(nujol), 1770 and 1680 cm^{-1}.

<u>Benzoquinone-2,5-disulfonic acid</u> Oxidation of the hydroquinone was attempted by two different methods:

(i) dichromate; 2.3 g of the disulfonic acid hydroquinone was dissolved in 80 ml of water, cooled to 17^{o}C, then treated with 0.80 ml of conc. sulfuric acid. An aqueous solution of 1.3 g of potassium dichromate in minimal water was added dropwise, with stirring and temperature control. No deposition of product when allowed to come to room temperature. Continuous extraction with ether yielded no product, even with NaCl saturation of the aqueous layer.

(ii) manganese dioxide; 2.5 g of the disulfonic acid hydroquinone was dissolved in 100 ml of 80% ethanol, then treated with 12.1 g of activated MnO_2, with stirring continuing at room temperature under nitrogen overnight. TLC's on silica: with methylene chloride, all R_f's= 0.0; with acetonitrile, R_f of starting material is 0.66, of MnO_2 treated product, 0.66 and 0.84. Mixture filtered through Celite plug and washed with methylene chloride; evaporation of solvent under reduced pressure with temperature control below 50°C. IR compared and contrasted with standard spectra for starting material and 2-hydroxy-benzene-sulfonic acid: 3210 and 1630 cm^{-1} with a broad 3600-3200 cm^{-1} stretch is consistent with the presence of intermolecular hydrogen bonding from sulfonic acid proton to ring carbonyl peaks.

Benzoquinone(hydroquinone)-2,5-disulfonyl chloride 1.0 g of the MnO_2 oxidation product was treated with 3.27 g of PCl_5 at 100°C for 5 hours. Quenching with ice, suction filtration and washing with water resulted in a partitioning of components when a methylene chloride extraction of the aqueous layer was tried. The methylene chloride-soluble component had a mobile spot on silica TLC that moved with the solvent line. Column chromatography of all methylene soluble fractions led to the isolation of a small amount of material with an IR having an extra 1730 cm^{-1} stretch, and a strong absorption at 730 cm^{-1}. The aqueous fraction showed anhydride formation upon evaporation of solvent.

(D) CYCLODEXTRIN CAPPING

(1) General procedure

All capping reactions were carried out in pyridine, under a nitrogen atmosphere. After addition of cyclodextrin, water may be removed by azeotropic distillation(94^{o}C, 59% water), and upon cooling to 50-60^{o}C, the capping agent may be added in the desired stoichiometric ratio. After 1-2 hours of stirring at this temperature, the reaction mixture is cooled, and the pyridine evaporated under reduced pressure with temperature maintenance at 40^{o}C or lower. The solid residue is dissolved in a minimal volume of water, which is then added dropwise to a vigorously stirring solution of acetonitrile: water(6:1 for disulfonyl, 5:2 for dicarbonyl). The mixture is suction filtered, and the filtrate concentrated by evaporation under reduced pressure, again with temperature maintenance. The sample is passed through anion and cation exchange columns, concentrated to minimal volume, then run through reverse phase C_{18} in portions, with gradient elution by water:acetonitrile following the pattern: 100% water; then 1:15, 1:10, 1:5, 2:5, 1:1; and finally 100% acetonitrile. The proposed monocap is located among the reverse phase fractions by thin layer chromatography on silica with vanillin staining. Final isolation and purification of the selected fraction is achieved by repeated column chromatography with silica and a gradient elution by water:acetonitrile following the pattern: 6:1, 5:1, 5:2, 5:3, 5:4 and finally 100% water.

(2) Reaction Conditions

Table 4 gives the various concentration parameters used in this study, as well as the % yield, which represents the total amount of reacted material which is relatively uncontaminated by the capping agent or unmodified cyclodextrin. The ranges represent two calculations based on molecular weights of assumed monocap or dicap. Owing to the low solubility of the anthraquinone dicarboxylic acid chlorides in pyridine, Run 5 was done by dropwise addition of the capping agent dissolved in a minimal volume of benzene, although there was no gross change in yield from the heterogeneous conditions in Run 4. No attempt was made to recover unreacted cyclodextrin for a % conversion calculation.

Table 4. Reaction Conditions: Quinone-capped Cyclodextrin

Capping reagent	Run#	conc.10^{-3}M	[CD]10^{-3}M	% yield
AQ-2,6-disulfonate	(1)	18.4	19.3	34-42
	(2)	21.9	17.5	35-43
	(3)	41.6	15.9	31-39
AQ-2,7-dicarboxylate	(4)	15.7	17.1	13-22
AQ-2,6-dicarboxylate	(5)	14.9	17.6	11-18
AQ-2,6(7)-dicarboxylate	(6)	46.3	17.7	7-9

(3) Chromatography

The use of vanillin staining and several solvent systems led to highly reproducible results on silica TLC. In Table 6, R_f's are reported with two significant figures only in order to distinguish between closely associated species; they represent average values of several spottings.

All reported positions I-IV are UV active; Fraction(III), moving faster than cyclodextrin and staining with vanillin, represents the potential mono-cap and is characterized by the strongest observable UV activity. Fractions I and II did not stain with vanillin; the former may represent an artifact of the solvent systems using ethyl acetate or tert-butylalcohol, which can complex with cyclodextrin. Fractions IV and V stain with vanillin and move slower than cyclodextrin, perhaps representing lower molecular weight oligomers.

Table 5. Thin-layer Chromatography

Solvent System	Retardation Factor [CD]	I	II	**III**	IV	V
Anthraquinone-2,6(2,7)-dicarboxylate/cyclodextrin						
n-PrOH:EtoAc:H_2O	3:5:1 [0.00]	0.51	0.13			
	6:5:3 [0.12]	0.76	0.64	**0.45**	0.39	0.09
t-ButOH:EtOH:H_2O	5:4:3 [0.60]		0.69	**0.38**	0.11	
n-PrOH:t-ButOH:H_2O	5:4:3 [0.32]		0.65	**0.39**	0.09	
n-PrOH:EtOh:H_2O	5:4:3 [0.71]		0.84	**0.81**	0.48	
CH_3CN:H_2O	5:1 [0.00]		0.31	**0.07**		
	5:2 [0.14]		0.57	**0.48**	0.11	
	5:3 [0.38]		0.75	**0.66**	0.26	
	5:4 [0.59]		0.80	**0.68**	0.51	
Anthraquinone-2,6-disulfonate/cyclodextrin						
n-PrOH:EtoAc:H_2O	3:5:1 [0.00]	0.50	0.90			
	6:5:3 [0.12]	0.7	0.74	**0.15**	0.09	0.05
t-ButOH:EtOH:H_2O	5:4:3 [0.60]	0.90	0.84	**0.76**	0.25	0.10
CH_3CN:H_2O	6:1 [0.00]	0.74	0.63	**0.21**		
	5:1 [0.00]		0.71	**0.33**		
	4:1 [0.00]		0.78	**0.59**		

(4) Spectral Data

Anthraquinone-2,6(2,7)-dicarboxylate/B-cyclodextrin

^{1}H NMR(D_2O, 60^{o}C): Figure 29a;

δ_{ppm}=9.0-8.0(aromatic, 6H); 4.9(anomeric, 7H).

^{13}C NMR(DMSO-d6, 60^{o}C):

Some evidence of δ_{ppm}=191, 186, 156, 153, 149, 98, 73 although not far enough above noise to make definite assignments.

IR(KBr): Figure 31a;

1680 cm^{-1}(v_{CO}, quinone);

1720 cm^{-1}(v_{CO}, ester carbonyl).

UV(3:2 MeOH:H_2O): Figure 32a;

λ_{max}(log ϵ)=333nm(3.78), 261nm(4.60).

Anthraquinone-2,6-disulfonate/B-cyclodextrin

^{1}H NMR(D_2O, 60^{o}C): Figure 29b;

δ_{ppm}=8.7-7.6(aromatic, 6H); 4.9(anomeric, 7H).

^{13}C NMR(DMSO-d6, 60^{o}C):

δ_{ppm}=134; 103, 83, 73, 61(broad);

some evidence of 183, 155, 128.

IR(KBr): Figure 31b;

1680 cm^{-1}(v_{CO}, quinone);

1370 and 1160 cm^{-1}(v_{OSO}).

UV(3:2 MeOH:H_2O,): Figure 32b;

λ_{max}(log ϵ)=334nm(3.71), 258nm(4.42).

NOTES

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VITA

Michael Vernie Cossette

Born in Norfolk, Virginia, May 30, 1956. Graduated from Norfolk Catholic High School in June 1974; B.S. in Biology, with dual major in History from the College of William and Mary in May 1978.

In September of 1983, the author re-entered the College of William and Mary as a post-baccalaureate, with studies in religion, philosophy and mathematics. Work as a graduate assistant in the Department of Chemistry began in August of 1986.