
**Supramolecular Chemistry**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

# Solubilization and electrochemical stabilization of substituted phenols through the use of 2-hydroxypropyl-β-cyclodextrin

Marcus E. Brewster[ab]; Andrew J. Braunstein[bc]; Michael Scott M. Bartruff[bd]; Chris Kibbey[ab]; Ming-Ju Huang[ab]; Emil Pop[ab]; Nicholas Bodor[ab]
[a] Pharmos, Corp., Two Innovation Dr., Suite A, Alachua, FL [b] Center for Drug Discovery, College of Pharmacy, University of Florida, Gainesville, FL [c] Southeastern College of Medicine, Miami, FL [d] Mercer University, Macon, GA

**To cite this Article** Brewster, Marcus E. , Braunstein, Andrew J. , Bartruff, Michael Scott M. , Kibbey, Chris , Huang, Ming-Ju , Pop, Emil and Bodor, Nicholas(1994) 'Solubilization and electrochemical stabilization of substituted phenols through the use of 2-hydroxypropyl-β-cyclodextrin', Supramolecular Chemistry, 4: 1, 69 — 76
**To link to this Article: DOI:** 10.1080/10610279408029864
**URL:** http://dx.doi.org/10.1080/10610279408029864

*SUPRAMOLECULAR CHEMISTRY*, Vol. 4, pp. 69–76
Reprints available directly from the publisher
Photocopying permitted by license only



# Solubilization and electrochemical stabilization of substituted phenols through the use of 2-hydroxypropyl-β-cyclodextrin

MARCUS E. BREWSTER*, ANDREW J. BRAUNSTEIN§, MICHAEL SCOTT M. BARTRUFF△, CHRIS KIBBEY, MING-JU HUANG, EMIL POP and NICHOLAS BODOR

*Pharmos, Corp., Two Innovation Dr., Suite A, Alachua, FL, 32615 and Center for Drug Discovery, College of Pharmacy, University of Florida, Gainesville, FL 32610*

*(Received November 29, 1993)*



**The effect of 2-hydroxypropyl-β-cyclodextrin (HPβCD) on the aqueous solubility and electrochemical stability of 2-substituted, 2,6-disubstituted and 2,4,6-trisubstituted phenols was investigated. All substituted phenols demonstrated an increase in water solubility ranging from 1.8 to 200-fold (in 40% HPβCD solutions). Cyclic voltammetry of a selected phenol, 2,6-diisopropylphenol, indicated addition of HPβCD increased the peak anodic potential and reduced the peak current consistent with cyclodextrin complex formation. Semiempirical molecular orbital methods (AM1) were used to examine complex structure and energetics.**

## INTRODUCTION

2,6-Disubstituted and other phenols have evolved as an important class of biologically active compounds exerting actions as diverse as anesthesia (2,6-diisopropylphenol, propofol, Diprivan®)[1], inhibition of chemical and biological oxidation (2,6-di-*t*-butyl-4-methylphenol, BHT)[2], uncoupling of oxidative phosphorylation ((3,5-di-*t*-butyl-4-hydroxybenzylidene)malononitrile, SF 6847)[3] and as chemoprotectants in stroke and brain trauma (2,6-di-*t*-butyl-4-(ethylaminomethyl)phenol, LY231617)[4]. Unfortunately, these derivatives are lipophilic and poorly water-soluble complicating their use in many biomedical applications. While several technologies have been brought to bare on this problem including the use of organic co-solvents, electroneutral detergents such as Cremophor EL (polyoxyethylenated castor oil) and oil-in-water emulsions, significant limitations exist for these approaches meaning that a generally useful method for solubilization has yet to be described[1, 5, 6, 7]. In addition, phenols, by their nature undergo oxidation mediated by a variety of processes which reduces the active concentration of the substance.

An alternative technology for increasing the aqueous solubility of poorly-water soluble compounds and one which may also contribute to increased stability is the use of cyclodextrins[8, 9, 10, 11]. Cyclodextrins provide for physicochemical augmentation through dynamic inclusion complex formation in aqueous solutions[11]. β-Cyclodextrin is limited in its water solubility reducing its usefulness. Chemically modified cyclodextrins including 2-hydroxypropyl-β-cyclodextrin are highly water soluble yet retain the ability to form inclusion complexes[12, 13, 14]. These materials are compatible with biological systems and have been extensively examined as potential pharmaceutical excipient[15, 16, 17]. Given the ability of modified cyclodextrin to solubilize and stabilize a wide range of compounds, they were applied to 2-substituted (2-methyl and 2-ethyl, 2-isopropyl and 2-tert.-butylphenol), 2,6-disubstituted (2,6-dimethyl, 2,6-diisopropyl and 2,6-di-tert.-butylphenol) and 2,4,6-trisubstituted (2,6-di-tert.-butyl-4-methyl and 2,4,6-trimethylphenol) phenols.

## EXPERIMENTAL

### Materials and Methods

2-Hydroxypropyl-β-cyclodextrin (HPβCD) was obtained from Pharmos, Corp. and characterized by elec-

* To whom correspondence should be addressed
§ Current Address: Southeastern College of Medicine, Miami, FL
△ Current Address: Mercer University, Macon, GA

trospray mass spectrometry. The degree of substitution was 7.0. Phenols were obtained from Aldrich Chemical Co. and were used without further purification. Phase-solubility profiles were constructed by determining the solubility of the phenol in solutions containing various concentrations of HPβCD (5 to 40% w/v) and then plotting the molar concentration of phenol solubilized as a function of the molar concentration of HPβCD[22]. In this process, solutions were made using water that has been boiled for 30 min and then cooled under a nitrogen atmosphere. An excess of a particular phenol was added to a solution of HPβCD at a particular concentration in an amber vial under an inert atmosphere and the vial was allowed to equilibrate for 48 h at ambient temperature (25°C). The vials were centrifuged and the supernatant filtered through 0.22 μm polyvinylidene difluoride membranes. The solutions were then analyzed by UV spectrophotometry. Standard curves for phenols were prepared in methanol and were linear ($r > 0.9999$) over the concentration range examined. The following wavelengths were used ($\lambda_{max}$): phenol (274 nm), 2-methylphenol (276 nm), 2-ethylphenol (276 nm), 2-isopropylphenol (276 nm), 2-tert.-butylphenol (274 nm), 2,6-diethylphenol (274 nm), 2,6-diisopropylphenol (274 nm), 2,6-di-tert.-butylphenol (272 nm), 2,6-di-tert.-butyl-4-methylphenol (280 nm) and 2,4,6-trimethylphenol (282 nm). Aqueous solubilities ($S_o$) and stability constants ($K_{1:1}$) were estimated from the solubility data ([M] of HPβCD versus [M] of phenol solubilized) by two approaches[18, 19]. In the first, the initial linear portion of the phase-solubility curve was fitted to a straight line. The y-intercept gives the $S_o$ and the $K_{1:1}$ was obtained by the following equation:

$$K_{1:1} = \frac{\text{slope}}{S_o(1-\text{slope})}$$

Alternatively, the phase-solubility relationship was fitted to a quadratic equation of the form:

$$S_t = S_o + K_{1:1}S_o[HP\beta CD] + K_{1:1}K_{1:2}S_o[HP\beta CD]$$

where $S_t$ is the total phenol solubilized and the y-intercept, again, gives the aqueous solubility.

Cyclic voltammetry of 2,6-diisopropylphenol was performed using a 1.0 mM solutions of the phenol prepared in 0.1 M $KH_2PO_4$ (pH 5). All determinations were made at ambient temperature in amber vials. After each scan, the glassy carbon electrode was effectively passivated due to deposition of oxidation products at the electrode surface. After each determination, the electrode was polished with alumina powder (0.3 μm) and cleaned with deionized water and acetonitrile.

### Equipment

UV spectra were obtained using either a Hewlett Packard HP8451A diode array or a Shimadzu UV-160 rapid scan spectrophotometer. Cyclic voltammagrams were recorded on a BAS Model CV-1B Cyclic Voltammograph connected to a Houston Instruments Omnigraphic X-Y 100 recorder. Solutions were degassed with argon prior to all determinations. Buffered phenol solutions were scanned at 100 mV/sec using a glassy carbon working electrode and a Ag/AgCl reference electrode at 10 μA/V sensitivity.

### Molecular Orbital Calculations and Parameter Estimation

Molecular orbital calculations were performed using the AM1 method[20, 21] which was installed on the Tektronix CAChe® (Version 2.8) workstation, a reactivity modeling system designed around the Apple Macintosh. Structures were generated using the resident templates in the CAChe® molecular editor and were minimized using the MM2 molecular mechanics package. The resulting files were then submitted for AM1 optimization wherein structures and energies (heats of formation ($\Delta H_f$) calculated at standard states in the gas phase in kcal/mol) were obtained by minimizing the total molecular energy with respect to all geometric variables using the Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization procedure[22]. The default SHIFT = 15 eV option was used to allow for 15 eV of damping on self-consistent field iterations to be determined by the rate of convergence and the PRECISE option was employed to tighten convergence criteria. Vertical ionization potentials were derived from the HOMO energy using Koopman's theorem[23]. Molecular renderings were produced with the aid of Chem 3D-plus (version 2.0.1.) software with Cartesian coordinates or z-matrices imported from the AM1 output files.

Molecular surface areas, volumes, ovalities, the $\log_{10}$ of the molar aqueous solubility and the $\log_{10}$ of the octanol-water partition coefficient were estimated using previously published techniques as described by Bodor[24, 25, 26]. Briefly, molecular volume (V) was calculated by a numerical integration technique in which a spherical grid systems is configured around the atom of interest. The volume is calculated from the following equation:

$$V = \frac{4}{3} r^3 \pi (n/n_t)$$

where r is the van der Waals radius, n is the number of grid points in the atomic volume and $n_t$ is the total number of grid points. The individual components are then summed to give the molecular volume. Similarly, surface area (S) is estimated by determining the grid points on the atomic surface (n), the total number of grid points and the van der Waals radius by the equation:

$$S = 4\pi n/n_t r^2$$

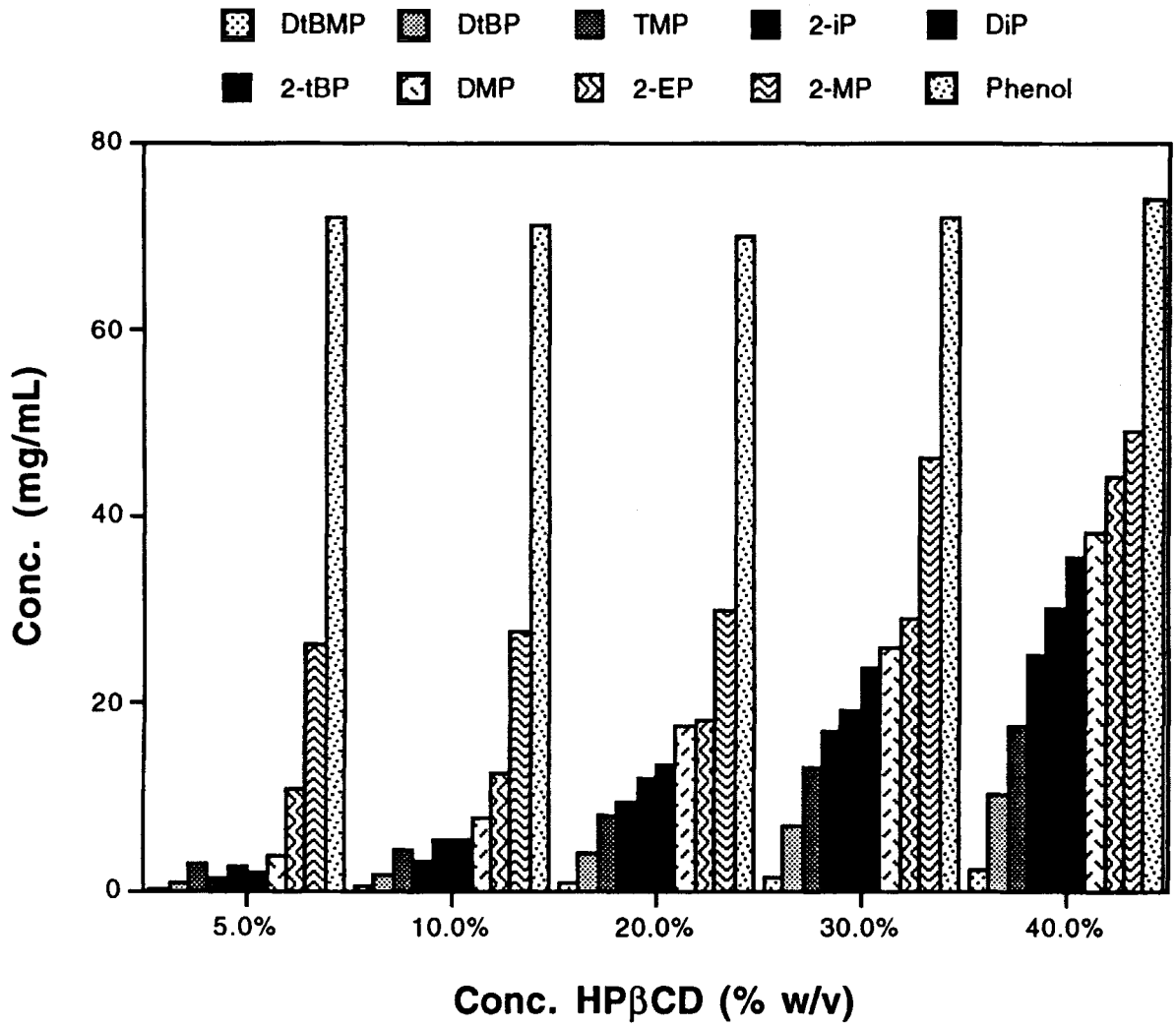



**Figure 1** Phase-Solubility Relationships for Phenol and Phenol Derivatives (DtBMP - 2,6-di-tert.-butyl-4-methylphenol, DtBP 2,6-di-tert.-butylphenol, TMP - 2,4,6-trimethylphenol, 2-iP 2-isopropylphenol, DiP - 2,6-diisopropylphenol, 2-tBP 2-tert.-butylphenol, DMP - 2,6-dimethylphenol, 2-EP - 2-ethylphenol, 2-MP - 2-methylphenol and phenol)

The atomic contributions are then summed to give the molecular surface area. The molecular ovality (O) is a ratio of the actual surface area to the minimum (spherical) surface and indicate the degree of spherical deviation. It is calculated from the equation:

$$O = s/4\pi\left(\frac{3V}{4\pi}\right)^{\frac{2}{3}}$$

## RESULTS

The increase in phenol solubility as a function of HPβCD concentration is collected in Figure 1 and Table 1. In most cases, HPβCD produces a clear increase in phenol solubility with the exception of phenol itself which has high intrinsic water solubility (70 mg/mL) and a relatively low stability ($K_{1:1}$) constant (94 $M^{-1}$ and 129 $M^{-1}$ for β-cyclodextrin[27, 28]). Of the remaining compounds, only 2-methylphenol and 2-ethylphenol had any

**Table 1** Phase-Solubility Parameters for Solubilization of Phenol and Substituted Phenols Including Aqueous Solubility ($S_o$), Stability Constant ($K_{1:1}$) and the Increase in Solubility upon Cyclodextrin Complexation (in a 40% w/v Solution).

| | | | *Increased Solubility* |
|---|---|---|---|
| *Compound* | $S_o$ *[M]* | $K_{1:1}$ *($M^{-1}$)* | *(Sol. in 40%/$S_o$)* |
| Phenol | 0.851 | -ND- | 0.98 |
| 2-Methylphenol | 0.225 | 71 | 2.01 |
| 2-Ethylphenol | 0.078 | 74 | 5.18 |
| 2-isopropylphenol | 0.010 | 176 | 18.51 |
| 2-tert.-butylphenol | 0.005 | 107 | 49.58 |
| 2,6-Dimethylphenol | 0.026 | 301 | 4.96 |
| 2,6-Diisopropylphenol | 0.002 | 226 | 96.77 |
| 2,6-Di-tert.-butylphenol | 0.0002 | 252 | 200.00 |
| 2,4,6-Trimethylphenol | 0.014 | -ND- | 8.37 |
| 2,6-Di-tert.-butyl-4-methylphenol | 0.0002 | 292 | 53.75 |

ND - not determined

**Table 2** Aqueous Solubility for Phenol and Substituted Phenols Determined from Phase Solubility Techniques or Estimated logW and Estimated Lipophilicity (log of the Octanol-Water Partition Coefficient, logP).

| *Compound* | $S_o$ *(mg/mL)* | *Est. logW (mg/mL)* | *Est. logP* |
|---|---|---|---|
| Phenol | 72.0[a] | 109 | 1.30[e] |
| 2-Methylphenol | 24.3[b] | 30 | 1.73[f] |
| 2-Ethylphenol | 8.5[c] | 9.6 | 2.15[g] |
| 2-isopropylphenol | 1.35 | 3.5 | 2.55 |
| 2-tert.-butylphenol | 0.72 | 0.99 | 2.86 |
| 2,6-Dimethylphenol | 3.53[d] | 12.92 | 2.14[h] |
| 2,6-Diisopropylphenol | 0.31 | 0.25 | 3.55 |
| 2,6-Di-tert.-butylphenol | 0.05 | 0.04 | 3.90 |
| 2,4,6-Trimethylphenol | 2.09 | 4.4 | 2.58 |
| 2,6-Di-tert.-butyl-4-methylphenol | 0.04 | 0.03 | 4.08 |

Literature values [a]66.7 mg/mL, [b]25 mg/mL, [c]3.52 mg/mL and [d]5.32 mg/mL.[42]
Literature Values [e]1.22-1.90, [f]1.92, [g]2.40 and [h]2.33.[43]

significant water solubility (25 mg/mL and 8.5 mg/mL, respectively) with other values below 2 mg/mL. Most solubility relationships were curvilinear demonstrating an $A_L$-type profile as defined by Higuchi and Connors[18]. This would suggest that at higher cyclodextrin concentration, higher order complexes form. Estimated stability constants are presented in Table 1 along with aqueous solubilities and increased solubilities of the phenol in the presence of a 40% (w/v) solution of HPβCD. The solubility of phenol derivatives in cyclodextrin indicated the following rank order: phenol > 2-methylphenol > 2-ethylphenol > 2,6-dimethylphenol > 2-tert.-butylphenol > 2,6-diisopropylphenol > 2-isopropylphenol > 2,4,6-trimethylphenol > 2,6-di-tert.-butylphenol > 2,6-di-tert.-butyl-4-methylphenol.

The water solubility and lipophilicity were estimated using a nonlinear model based on parameters derived from the AM1 semiempirical molecular orbital approach[24, 25]. These results as well as experimental and literature data are presented in Table 2. Other calculated properties including the vertical ionization potentials, molecular volume, surface area and ovality are presented in Table 3 while molecular dimensions of phenol and the phenolic derivatives are shown in Table 4. As expected, increased molecular complexity introduced by homologue extension increase the lipophilicity of the phenol and decrease the water solubility. The molecular ovality indicated increasing deviation from a spherical minimum surface with the highest value associated 2,6-di-tert.-butylphenol. Finally, while substitution does not dramatically alter the width of the phenyl tail, the region associated with the 2-substitution or 2,6-disubstituted portion is augmented. The effective width of the phenol head is increased from 6.4 Å in phenol to 11.4 Å in 2,6-di-tert.-butylphenol. Proposed orientations for the phenols in the cyclodextrin cavity are depicted in Figures 2, 3 and 4.

The electrochemical behavior of a selected phenol, 2,6-diisopropylphenol, in the presence or absence of HPβCD was examined. 2,6-Diisopropylphenol, in common with other members of this chemical class, demonstrated irreversible oxidation on glassy carbon and a single anodic scan resulted in passivation of the working electrode surface. Thus, electrode reconditioning was required after each determination. As illustrated in Figures 5, the addition of HPβCD resulted in two characteristic changes in the cyclic voltammagrams: the peak anodic potential ($E_p$) were shifted to greater positive values (1.6 ± 0.25 mV at 1.0 mM HPβCD and 5.7 ± 0.31 mV at 5.0 mM HPβCD) and the peak currents were reduced.

## DISCUSSION

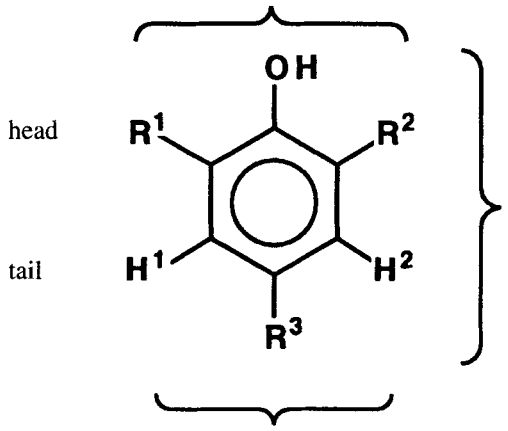
The solubility of phenol and the phenol derivatives were increased in the presence of HPβCD with marginal effects on the phenol itself and the most dramatic effects on 2,6-di-tert.-butylphenol which showed a 200-fold increased in water solubility in a 40% HPβCD system. Derived stability constants were highest for the 2,6-disubstituted phenols and these values were increased (in the case of 2,6-di-tert.-butylphenol) by 4-methylation. Such effects have been observed in the case of phenol which binds more tightly to β-cyclodextrin when 4-methylated[27]. The collected data are very similar to those

**Table 3** Selected Energetic (Heat of Formation ($\Delta H_f$, Kcal/Mol), Electronic (Vertical Ionization Potential, I.P.) and Geometrical (Molecular Volume, Å$^3$, Molecular Surface Area, Å$^2$ and Ovality) Properties of Phenol and Substituted Phenols Estimated Using the AM1 Molecular Orbital Approximation.

| *Compound* | $\Delta H_f$ *Kcal/mol* | *Vert. I.P. eV* | *Vol. Å$^3$* | *S. Area Å$^2$* | *Ovality* |
|---|---|---|---|---|---|
| Phenol | -22.25 | 9.12 | 91.8 | 120.5 | 1.22 |
| 2-Methylphenol | -29.01 | 8.96 | 108.4 | 141.2 | 1.284 |
| 2-Ethylphenol | -34.45 | 8.94 | 125.1 | 161.1 | 1.33 |
| 2-isopropylphenol | -38.07 | 8.97 | 141.8 | 181.2 | 1.38 |
| 2-tert.-Butylphenol | -38.33 | 8.96 | 157.6 | 194.6 | 1.38 |
| 2,6-Dimethylphenol | -34.97 | 8.89 | 124.6 | 159.8 | 1.33 |
| 2,6-Diisopropylphenol | -53.15 | 8.87 | 191.0 | 237.5 | 1.48 |
| 2,6-Di-tert.-butylphenol | -50.52 | 8.88 | 223.2 | 267.8 | 1.51 |
| 2,4,6-Trimethylphenol | -42.46 | 8.70 | 141.4 | 181.6 | 1.38 |
| 2,6-Di-tert.-butyl-4-methylphenol | -59.61 | 8.67 | 239.5 | 287.8 | 1.48 |

**Table 4** Selected Intramolecular Distances (Including van der Waals Radii) for Phenol and Phenol Derivatives.

b = $R^1$ − $R^2$ distance + (2 × van der Waals radii) in Å




c = H − $R^3$ distance + (2 × van der Waals radii) in Å

a = $H^1$ − $H^2$ distance + (2 × van der Waals radii) in Å

| *Compound* | *a* | *b* | *c* |
|---|---|---|---|
| Phenol | 6.4 | 6.4 | 7.9 |
| 2-Methylphenol | 6.4 | 7.7 | 7.9 |
| 2-Ethylphenol | 6.4 | 8.9 | 7.9 |
| 2-isopropylphenol | 6.4 | 8.7 | 7.9 |
| 2-tert.-butylphenol | 6.4 | 8.9 | 7.9 |
| 2,6-Dimethylphenol | 6.5 | 9.0 | 7.9 |
| 2,6-Diisopropylphenol | 6.4 | 10.8 | 7.9 |
| 2,6-Di-tert.-butylphenol | 6.3 | 11.4 | 7.9 |
| 2,4,6-Trimethylphenol | 6.4 | 8.9 | 8.6 |
| 2,6-Di-tert.-butyl-4-methylphenol | 6.4 | 11.4 | 8.6 |



obtained using the parent, β-cyclodextrin suggesting that the added hydroxypropyl functions do not significantly change the binding dynamics. Other data comparing large numbers of complex stability constants for compounds with either β- or hydroxypropyl-β-cyclodextrin corroborate, in large part, this observation[29].

Several general molecular properties are associated with increasing complex formation including lipophilicity. Estimated log P values generally, therefore, were found to correlate with increasing $K_{1:1}$ values. In addition, since the forces that hold the guest and host together are van der Waals in nature, maximization of contact between the phenol and the cyclodextrin cavity will enhance complexation[11]. The diameter of the β-cyclodextrin torus is 7.8Å while the molecular volume is reported to be 346 Å$^3$ [11]. Based on calculated molecular volumes for the phenol derivatives, all have small molecular volumes similar to that of the cyclodextrin cavity ranging from 92 to 240 Å$^3$. The interatomic distances however present restrictions to cyclodextrin interaction. Thus, while phenol and 2-methylphenol could conceivable fit into the wider opening of the cyclodextrin molecule, the bulk of the other 2-substituted or 2,6-disubstituted phenols would preclude complete engulfment by the cavity. The effective width of this portion of the molecule increases from 8.9 Å in the case of 2-ethylphenol to 11.4 Å in the case of 2,6-di-tert-butylphenol. This would suggest, as illustrated in Figures 2, 3, and 4, an orientation in which the unsubstituted portion of the phenyl group (C3, C4 and C5) is included into the cyclodextrin cavity. This assignment is also consistent with the observation that phenyl substituent can interact with a small substituent oriented toward the cavity (head first) or positioned away from the cavity (tail first) but never crosswise and with various NMR results[11, 30]. Methylation of the 4-position of these substituted phenols does not inhibit complex formation and may be beneficial by increasing the effective surface area for interaction. These effects appear to operate in the case in 2,6-di-tert.-butyl-4-methylphenol.

Electrochemically, while phenoxides undergo facile one-electron oxidation to form the phenoxy radical, the mechanism of oxidation of protonated phenol is less clear with two historical arguments forwarded: sequential electron-proton-electron transfer and a synchronous bielectronic transfer[31, 32, 33]. Papouchado et al. found that the cyclic voltammagram of phenol is characterized by a single primary oxidation peak[34]. At low anodic potential, phenol dimerization occurs and this process is so rapid that it competes with the second electron transfer. At higher potentials, a two-electron process is predominant. Whether this two-electron process is concerted or se-

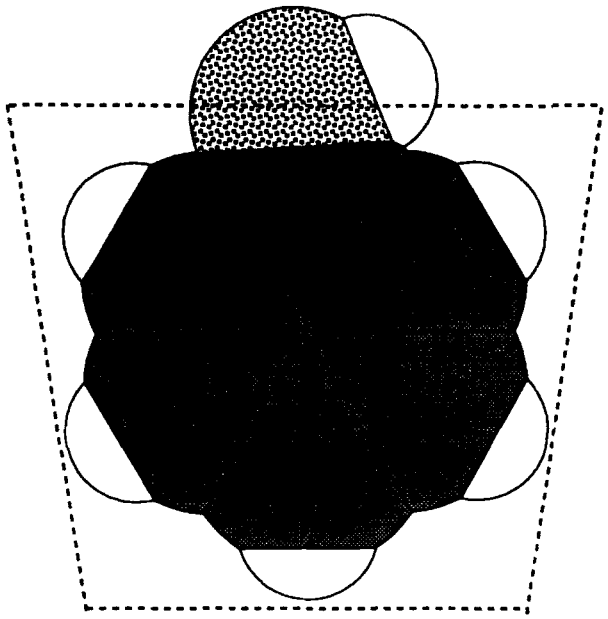


**Figure 2** Suggested Orientation of Phenol in the β-Cyclodextrin Cavity based on Modeling and NMR Studies.[30]



quential is difficult to evaluate in phenol but in napthol, it can be clearly divided into two well-defined reactions. This and other factors suggest that the two-electron oxidation of phenols is actually composed of two closely spaced electron transfers[34]. The oxidation of 2,6-disubstituted phenols follow similar patterns. In the case of 2,6-dimethylphenol, a two-electron anodic oxidation was suggested based on the electrochemical products isolated which were indicative of a phenoxonium intermediate[35].

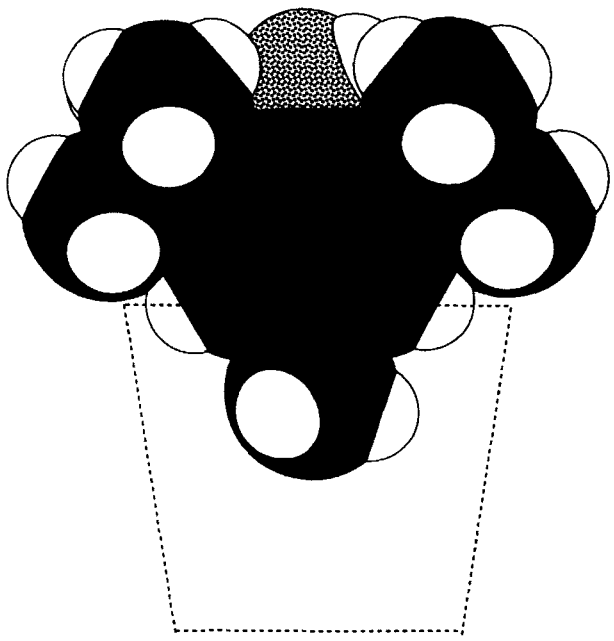


**Figure 4** Suggested Orientation of 2,6-Di-tert.-butyl-4-methylphenol in the β-Cyclodextrin Cavity.

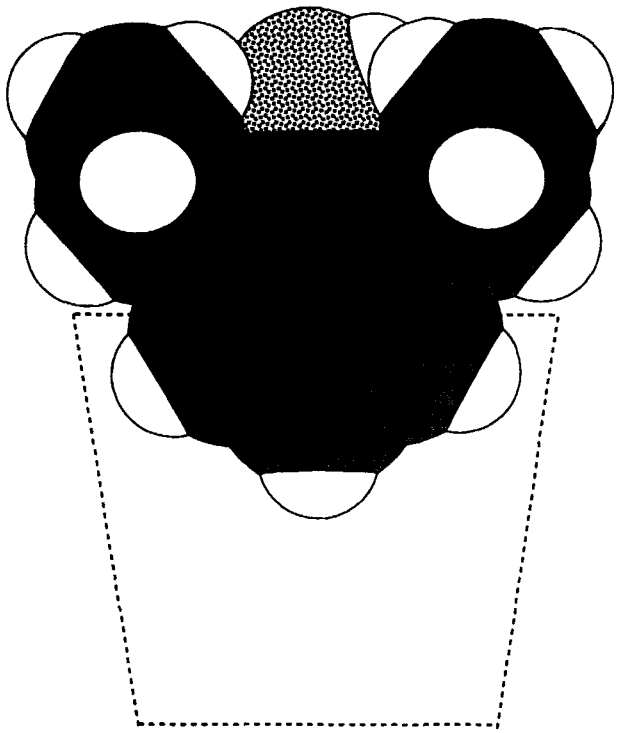


**Figure 3** Suggested Orientation of 2,6-Diisopropylphenol in the β-Cyclodextrin Cavity

The electrochemical oxidation of 2,6-di-tert.-butyl-4-methylphenol also demonstrates a two-electron oxidation which is likely made up of two one-electron oxidations separated by a proton transfer[36].

The general electrochemical behavior of 2,6-diisopropylphenol was not substantially altered by addition of HPβCD to aqueous buffered solutions (pH 5). Two changes were however evident including a small increase in the anodic peak potential ($E_p$) to higher positive values and a decrease in the peak current ($i_p$) (Figure 5). The change in peak current can be related to a number of phenomenon including a change in the diffusion coefficient of the analyte[37, 38, 39, 40]. Such a change in diffusivity could occur due to increased solution viscosity, however, the concentration of HPβCD used (1.0 mM and 5.0 mM) was well below those known to increase or alter this parameter[37]. The change in peak current may be related to changes in the electrode surface associated with surface polishing, but consistent peak currents and potentials were obtained after multiple scans. The change is peak currents may also be related to the lowering of the diffusion coefficient of the phenols which results upon HPβCD complex formation. Takamura et al. found that in the electrochemically mediated oxidation of chlorpromazine, complex formation with β-cyclodextrin resulted in a lowering of the diffusion coefficient as measured by electroconductivity and in an increase in Stokes' diameter of the compound[41]. Examination of the electrochemical behavior of other cyclodextrin-encapsu-

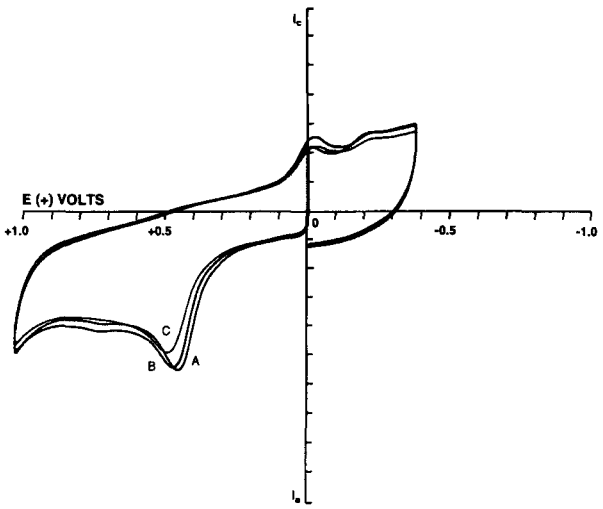



**Figure 5** Cyclic Voltammagrams for 2,6-Diisopropylphenol. For this compound, A refers to a 1.0 mM solution of the phenol in phosphate buffer (pH 5), B to a 1.0 mM solution of the phenol in a 1.0 mM buffered solution of HPβCD and C to a 1.0 mM solution of the phenol in a 5 mM buffered solution of HPβCD. Samples were scanned at 100 mV/sec using a glassy carbon working electrode relative to a Ag/AgCl reference electrode at 10 μA/V. For 2,6-diisopropylphenol, a 1.0 mM solution of HPβCD resulted in a 1.6 ± 0.25 mV shift of the peak oxidation potential to higher voltage and the 5.0 mM HPβCD solution, a shift of 5.7 ± 0.31 mV to greater positive potential. Data reflect the mean and SEM for three experiments.

lated systems show similar changes in peak current which have been used to estimate stability constants and other thermodynamic information[40]. Importantly such determination can only be made with reversible systems when cyclic voltammetry is applied since the limiting diffusion current is not accounted for in this technique[40].

The change in peak potential could be caused by several factors. If HPβCD interacts with 2,6-diisopropylphenol such that the electrochemically active portion of the molecule is either included or only partially included, the electron transfer process may be hindered. If this interaction reduces the oxidation efficacy by, for example, conformational changes that increase the molecular vertical or adiabatic ionization potential, the peak potential will be shifted to higher values. This process has been used to explain the electrochemical reactivity of several systems including the cyclodextrin complex of chlorpromazine[41]. On the other hand, the changes in the relative oxidation and reduction potentials for ferrocene derivatives and related systems in cyclodextrin solutions suggest that dissociation must occur prior to oxidation pointing to an EC-type mechanism[38]. In this circumstance, the electrochemically active portion of the molecule is buried in the cyclodextrin cavity. Since the oxidation of phenols is not reversible, it is not possible to gauge the difference in the oxidation and reduction peaks which would provide evidence for a requisite decomplexation prior to oxidation[38]. Qualitatively, the parameters here are similar to those described by the oxidation of chlorpromazine. In addition, the aforementioned model studies suggest that the phenolic oxygen is exposed and may be available for interaction with the electrode surface. In any case, the data suggest stabilization of the phenols i.e., an increased anodic potential, to electrochemically mediated oxidation. Such a characteristic would be helpful in providing stable forms of the phenols of interest.

In summary, HPβCD was found to readily solubilize a number of biologically and chemically important phenols in a curvilinear manner. Solutions of the phenols in cyclodextrin were resistant to electrochemical oxidation as illustrated by increased anodic peak potentials. Such stability could well translate into decreased lability toward other oxidative process.

## REFERENCES


1 P. Sebel and J. Lowdon: *Anesthesiology*, **1989**, *71*, 260.
2 G. Hocman: Int. *J. Biochem.*, **1988**, *20*, 639 .
3 K. Yoshikawa and H. Terada: *J. Am. Chem. Soc.*, **1982**, *104*, 7644.
4 J. McCall and J. Panetta: *Ann. Rept. Med. Chem.*, **1992**, *27*, 31.
5 J. Glen: Br. *J. Anaesth.*, **1980**, *52*, 731.
6 M. Ennis, W. Lorenz and W. Gerland: *Ag. Actions.*, **1986**, *18*, 235.
7 J. Gaudy, J. Sicard, F. Lhost and J. Boitier: *Can. J. Anaesth.*, **1987**, *34*, 122.
8 J. Pagington: *Chem. Brit.* **1987**, 455.
9 J. Lach and J. Cohen: *J. Pharm. Sci.*, **1963**, *52*, 137.
10 W. Saenger: *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 344.
11 J. Szeftli: *Cyclodextrins and Their Inclusion Complexes*, Akadémiai Kiadó, Budapest, **1982**.
12 J. Pitha, J. Milecki, H. Fales, L. Pannell and K. Uekama: *Int. J. Pharm.*, **1986**, *29*, 73.
13 A. Yoshida, H. Arima, K. Uekama and J. Pitha: *Int. J. Pharm.*, **1988**, *46*, 217.
14 B. Muller and U. Brauns: *Int. J. Pharm.*, **1985**, *26*, 77.
15 J. Pitha, M. Harman and M. Michel: *J. Pharm. Sci.*, **1986**, *75*, 165.
16 M. Brewster, K. Estes and N. Bodor: *Int. J. Pharm.*, **1990**, *59*, 231.
17 J. Mesens, P. Putteman and P. Verheyen: *New Trends in Cyclodextrins and Derivatives*, D. Duchêne (Ed.), Editions de Santé, Paris, **1991**, pp. 371-407.
18 T. Higuchi and K. Connors: *Adv. Anal. Chem. Instrum.*, **1965**, *4*, 117.
19 Brewster, J. Simpkins, M. Hora, W. Stern and N. Bodor: *J. Parent. Sci. Technol.*, **1989**, *43*, 231.
20 M. Dewar, E. Zoebish, E. Healy and J. Stewart: *J. Am. Chem. Soc.*, **1985**, *107*, 3902.
21 M. Dewar and J. Storch: *J. Am. Chem. Soc.*, **1985**, *107*, 3898.
22 J. Head and M. Zerner, *Chem. Phys. Lett.*, **1985**, *122*, 264.
23 T. Clark: *A Handbook of Computational Chemistry*, Wiley, New York, **1985**.
24 N. Bodor, Z. Gabanyi and C. Wong: *J. Am. Chem. Soc.*, **1989**, *111*, 3783.
25 N. Bodor and M. Huang: *J. Pharm. Sci.*, **1992**, *81*, 954.
26 N. Bodor, A. Harget and M. Huang: *J. Am. Chem. Soc.*, **1991**, *113*, 9480.
27 G. Bertrand, J. Faulkner, S. Han and D. Armstrong: *J. Phys. Chem.*, **1989**, *93*, 6863.
28 A. Buvári and L. Barcza: *J. Chem. Soc., Perkin Trans. II*, **1988**, 543.
29 K. Uekama and M. Otagiri: *CRC Crit. Rev. Therap. Drug Carrier Sys.*, **1987**, *3*, 2.
30 Y. Inoue, T. Okuda, Y. Miyata and R. Chûjô: *Carbohydr. Res.*, **1984**, *125*, 65.
31 M. Ciureanu, J. Herdan, A. Balaban: *Rev. Roum. Chim.*, **1989**, *34*, 739.
32 J. Hedenburg and H. Freiser: *Anal. Chem.*, **1953**, *25*, 1355.

33 V. Gaylor, A. Conrad and J. Landerl: *Anal. Chem.*, **1957**, *29*, 224.
34 L. Papouchado, R. Sanford, G. Petrie and R. Adams: *J. Electroanal. Chem.*, **1975**, *65*, 275.
35 N. Oyama, T. Ohsaka, Y. Ohnuki and T. Suzuki: *J. Electrochem. Soc.*, **1987**, *134*, 3068.
36 A. Ronlán and V. Parker: *J. Chem. Soc. (C)*, **1971**, 3214.
37 T. Matsue, D. Evans, T. Osa and N. Kobayashi: *J. Am. Chem. Soc.*, **1985**, *107*, 3411.
38 R. Isnin, C. Salam and A. Kaifer: *J. Org. Chem.*, **1991**, *56*, 35.
39 A. Diaz, P. Quintela, J. Schuette and A. Kaifer: *J. Phys. Chem.*, **1988**, *92*, 3537.
40 P. Bersier, J. Bersier and B. Klingert: *Electroanal.*, **1991**, *3*, 443.
41 K. Takamura, S. Inoue, F. Kusu, M. Otagoro and K. Uekama: *Chem. Pharm. Bull.*, **1984**, *32*, 839.
42 S. Valvani and S. Yalkowsky: Physical Chemical Properties of Drugs, S. Yalkowsky, A. Sinkula and S. Valvani (Eds.), Marcel Dekker, New York, **1980**, pp. 201-229.
43 A. Leo, C. Hansch and D. Elkins: *Chem. Rev.*, **1971**, *71*, 525.