electrostatic repulsion between the ionic segments of a HPAA molecule.

The Debye length in the absence of foreign salt is given by $(4\pi Bn)^{-1/2}$. Here, B denotes the Bjerrum length (0.719 nm at 25 °C in water) given by $e^2/\epsilon kT$, where e is the electronic charge, ϵ is the dielectric constant, and n is the concentration (cm^{-3}) of the free ("diffusible") counterions (H^+ ions). The concentrations of the protons of HPAA at $\alpha = 0$ are estimated to be 5.66×10^{-4} ([HPAA]) $\times$ 0.03 (θ) = 1.7×10^{-5} M and $5.34 \times 10^{-4} \times 0.03 = 1.6 \times 10^{-5}$ M for HPAA's of MW = 2×10^6 and 9×10^4, respectively. Thus, the D_1 values at $\alpha = 0$ are estimated to be ca. 100 nm. These values of D_1 are long compared with the monomer length (0.25 nm) and comparable with the contour lengths of HPAA (300 and 600 nm for HPAA's of MW = 9×10^6 and 2×10^6, respectively). It should be noted that the importance of the Debye length has been pointed out by some researchers for the solution properties of polyelectrolytes and deionized colloidal particles.[5,7,14,29-33] Note that pH values begin to increase when α values begin to increase from zero as is shown in Figure 7, which means that the dissociation occurs immediately on addition of NaOH to the HPAA solution. But, the conformation begins to expand in the negative range of α values.

In conclusion, viscometric studies show that the conformation of HPAA molecules in dilute solution is highly extended. This is so because of the very long Debye screening length that enhances the repulsive forces between charged carboxylates even at the low charge density of the polymer chain. By contrast, with polyelectrolytes such as NaPAA, the charge density is high, but the Debye screening length short, of the order of a few nanometers. Sheaths of electrical double layers are very soft and compressed or distorted easily by an external force and even by thermal motion of the polymer chain. It is plausible that the double layer is not sufficiently stable to remain homogeneously distributed around the macroion under shear flow. For linear-type polyelectrolytes, translational and rotational movements of the chain segments are considered to be much more vigorous compared with those of colloidal particles.[7] Further work especially on the solution properties of the macroions having very low charge densities is now in progress.

Acknowledgment. I am grateful to the Japanese Ministry of Education, Science and Culture for support of this work.

Registry No. HPAA, 9003-01-4; NaCl, 7647-14-5.

(29) Barenes, C. J.; Chan, D. Y.; Everett, D. H.; Yates, D. E. *J. Chem. Soc., Faraday Trans. 2* **1978**, *74*, 136.
(30) Giordano, R.; Maisano, G.; Mallamace, F.; Micali, N.; Wanderlingh, F. *J. Chem. Phys.* **1981**, *75*, 4770.
(31) Shaw, J. N.; Ottewill, R. H. *Nature (London)* **1984**, *208*, 681.
(32) Goff, J. R.; Luner, P. *J. Colloid Interface Sci.* **1984**, *99*, 468.
(33) Hachisu, S.; Kobayashi, Y.; Kose, A. *J. Colloid Interface Sci.* **1973**, *42*, 342.

Substituent Effects on the Binding of Phenols to Cyclodextrins in Aqueous Solution

Gary L. Bertrand,* James R. Faulkner, Jr., Soon M. Han, and Daniel W. Armstrong

Department of Chemistry, University of Missouri—Rolla, Rolla, Missouri 65401
(Received: January 23, 1989)

Equilibrium constants and standard enthalpies have been measured calorimetrically for the formation of complexes of α- and β-cyclodextrins with substituted phenols in aqueous solutions at 298.15 K. The study includes variation of the size and shape of the phenol, the size and degree of methylation of the cyclodextrin, and the effects of pH and ionic strength. Substituent effects were measured for *p*-chloro-, *p*-bromo-, *p*-methyl-, *p*-hydroxy-, *p*-nitro- and *m*-nitrophenols. The effects of ionization were studied with *m*- and *p*-nitrophenolate ions. The effects of methyl substitutions of β-cyclodextrin were investigated with nitrophenol and nitrophenolate ions complexing with heptakis(2,6-di-*O*-methyl)-β-cyclodextrin and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin. All of the effects studied show a substantial amount of entropic–enthalpic compensation, such that free energy effects are relatively small in comparison to enthalpic and/or entropic effects, but there was no simple relationship between the standard enthalpies and entropies of complex formation. However, a linear relationship was observed between the enthalpy and entropy for the transfer of substituted phenols from the complex with α-cyclodextrin to the complex with β-cyclodextrin. This relationship was independent of pH and ionic strength. In general, complex formation of a substituted phenol with α-cyclodextrin is more exothermic than with β-cyclodextrin, but the entropy of complex formation is also more negative.

Introduction

Complexation of organic molecules by cyclodextrins has been of great interest for analytical and preparative separations[1-3] and for controlling the path and products of organic syntheses.[4] For enantiomeric separations, the smallest of these host molecules, α-cyclodextrin, generally has been found to be selective toward single-ring aromatic compounds, while the larger β-cyclodextrin is more selective toward molecules containing two aromatic rings.[5] Equilibrium constants have been reported for many of these complexes[6-12] and enthalpies of formation have been reported for a few,[7,11] but there have been few systematic investigations of the effects of size, shape, and polarity on the thermodynamic parameters for complexation.

The "high-dilution" calorimetric technique was chosen for this study in order to simultaneously determine equilibrium constants and enthalpies of complex formation. This technique is more generally applicable to cyclodextrin complexes than the more conventional spectroscopic techniques, because of the very small

(1) Hinze, W. L. *Sep. Purif. Methods* **1981**, *10*, 159.
(2) Armstrong, D. W.; DeMond, W. *J. Chromatogr. Sci.* **1984**, *22*, 411.
(3) Jelinek, I.; Snopek, J.; Smolkova-Keulemansova, E. *J. Chromatogr.* **1987**, *405*, 379.
(4) (a) Liu, J. H.; Weiss, R. G. *J. Org. Chem.* **1985**, *50*, 3657. (b) Liu, J. H.; Weiss, R. G. *J. Photochem.* **1985**, *30*, 303. (c) Liu, J. H.; Weiss, R. G. *Isr. J. Chem.* **1985**, *25*, 228.
(5) Armstrong, D. W.; Yang, X.; Han, S. M.; Menges, R. *Anal. Chem.* **1987**, *59*, 2594.
(6) Cramer, F.; Saenger, W.; Spatz, H.-Ch. *J. Am. Chem. Soc.* **1967**, *89*, 14.
(7) Lewis, E. A.; Hansen, L. *J. Chem. Soc., Perkin Trans. 2* **1973**, 2081.
(8) Hall, E. S.; Ache, H. J. *J. Phys. Chem.* **1979**, *83*, 1805.
(9) Rymden, R.; Carlfors, J.; Stilbs, P. *J. Inclusion Phenom.* **1983**, *1*, 159-167.
(10) Inoue, Y.; Okura, T.; Miyata, Y.; Chujo, R. *Carbohydr. Res.* **1984**, *125*, 65.
(11) Barone, G.; Castronuova, G.; Del Vecchio, P.; Elia, V.; Muscetta, M. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 2089-2101.
(12) Buvari, A.; Barcza, L. *J. Chem. Soc., Perkin Trans. 2* **1988**, 543.

0022-3654/89/2093-6863$01.50/0

spectral shifts that have been found for many of these complexes. For the most accurate work, the calorimetric technique requires that one of the complexing components be reasonably soluble, so that a relatively concentrated solution can be injected into a more dilute solution of the other component. Ideally, the dilution of this solution in a "blank" solution would produce a small enthalpy effect, so that the enthalpy of dilution in a solution containing the other component will be primarily due to complexation. The limited solubility of the cyclodextrins (α, 0.114 M; β, 0.016 M) is a severe limitation to the study of weak complexes.

A series of phenols was chosen for this study because of the availability of comparison data from previous studies, sufficient solubility for a range of substituents of different sizes and polarities, and the possibility of studying both molecular and ionized forms of some members of the series. The existence of X-ray crystallographic data[13] relating to the "fit" of *p*-nitrophenol in the cavity of α-cyclodextrin was also an important consideration.

In their discussion of the binding forces in cyclodextrin inclusion complexes, Bender and Komiyama[14] focus primarily on the energetics of complex formation. Energy differences were also stressed in a theoretical treatment of enantiomeric separations by cyclodextrins.[15] Energy differences are certainly expected to play an important role, especially in the α-cyclodextrin cavity. However, a less restricted fit is expected in the case of β-cyclodextrin complexes with smaller adducts, and the weak complex ($K = 20 \pm 5$ L/mol) between 1-butanol and β-cyclodextrin was found to have a positive enthalpy of formation (4.5 ± 0.8 kJ/mol).[16] The systematic study of a series of similar compounds in both α- and β-cyclodextrins should yield important information regarding the interplay between entropic and enthalpic effects in the formation of these complexes.

Experimental Section

Materials. α- and β-cyclodextrins were from Advanced Separation Technologies, Inc. Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (no longer available) from Aldrich were used for most of the work reported here. Samples obtained from Chinoin Pharmaceutical and Chemical Works Ltd. gave very similar results. Eastman *m*-nitrophenol and Fisher *p*-nitrophenol were recrystallized from aqueous HCl solution, then twice recrystallized from ethanol, and dried under vacuum. Fisher "liquified" phenol was diluted to an appropriate concentration and then analyzed by conductimetric titration with standard sodium hydroxide. Eastman *p*-chlorophenol and *p*-bromophenol were used without further purification, as were *p*-cresol (Aldrich; 99+%) and hydroquinone (Baker). Hydroquinone solutions were used within 4 h of preparation, but a slight discoloration could be observed near the end of this period.

Phosphate buffers were prepared at an ionic strength of approximately 1.8 M from concentrated phosphoric acid and sodium hydroxide pellets and then adjusted with concentrated sodium hydroxide to give either pH 4.1 or 11.2 upon 10-fold dilution with distilled water. These concentrated buffers were then diluted volumetrically in preparation of cyclodextrin solutions or blank solutions. Checks on the pH of the solutions after calorimetric measurements showed values within 0.2 pH unit of the target values.

Calorimetry. All measurements were performed on a Tronac Model 550 titration calorimeter, operating in the isoperibol mode with the bath at 25.00 ± 0.02 °C. All measurements were within 0.1 °C of the bath temperature. Increments of 0.2–1.0 mL of phenolic solutions (0.1–0.2 M) were added to approximately 92 mL of cyclodextrin solutions (0.0005–0.015 M) from a 2.5-mL Gilmont micrometer buret, readable to 0.0002 mL. No concentration effects were observed for three or more injections into blank solutions.

Measurements on cyclodextrin solutions included two or more concentrations of the phenol at each of two or more concentrations of cyclodextrin, and each set included at least six measurements. While measurements were made for a series of injections, the incremental enthalpy effects were accumulated such that calculated values of the enthalpy effect per mole of added phenol were for addition of the total amount of phenol. This allows calculations of equilibrium constants and enthalpies of reaction based on the integral amount of complex formed, rather than a differential quantity.

Results

The complexation equilibrium donor (D) + acceptor (A) $\leftrightarrow$ complex (C) is studied calorimetrically in aqueous solution, specifically with the donor being a substituted phenol molecule or ion and the acceptor a cyclodextrin or derivatized cyclodextrin. Calorimetric measurements of ΔH_1 are made at different values of $n_D°$ and $n_A°$ for the process

$$n_D°\text{D (aq, [D]*, } T\text{)} + n_A°\text{A (aq, [A]*, } T\text{)} \rightarrow \{n_A\text{A}, n_D\text{D}, n_C\text{C}\}\text{ (aq, [A]°, [D]°, } T\text{)} \quad (1)$$

and ΔH_2 for the similar process for a solvent "blank":

$$n_D°\text{D (aq, [D]*, } T\text{)} + \text{H}_2\text{O} \rightarrow n_D°\text{D (aq, [D]°, } T\text{)} \quad (2)$$

The notation "aq" as used here may refer to water as solvent or a buffered solution, [A]* and [D]* are the formal concentrations of acceptor and donor before mixing, and [A]° and [D]° are the formal concentrations after mixing. Details of the calculational procedure are given in the Appendix. The experimental data were reduced to the enthalpy of transfer (H/L) of the substituted phenol from 1 L of the blank solution to the solution containing the cyclodextrin, as a function of [A]° and [D]°. A weighted least-squares procedure was used to find the "best" values of K and $\Delta_{rx}H°$ (and their statistical uncertainties) satisfying the following equations:

$$K = [\text{C}]/[\text{A}][\text{D}] = [\text{C}]/([\text{A}]° - [\text{C}])([\text{D}]° - [\text{C}]) \quad (3)$$

$$H/\text{L} = [\text{C}]\Delta_{rx}H° \quad (4)$$

Other thermodynamic parameters were then calculated from

$$\Delta_{rx}G° = -RT \ln K = \Delta_{rx}H° - T\Delta_{rx}S° \quad (5)$$

The results of these calculations are given in Table I for *p-nitrophenol and m-nitrophenol in unbuffered aqueous solutions* and for their anions in phosphate buffer solution at pH 11.1 and ionic strength of 0.9 M. Results for phenol and para-substituted phenols are given in Table II for phosphate buffer solutions at pH 4.2 and ionic strength of 0.18. The effects of ionic strength were investigated for phenol with α- and β-cyclodextrins, and for *p*-nitrophenolate ion with α-cyclodextrin. For the *p*-nitrophenolate ion, there was no significant effect of ionic strength on either the equilibrium constant or the enthalpy of complexation. In the case of phenol, there was no significant change in the equilibrium constant for β-cyclodextrin solutions with ionic strengths of 0, 0.18, and 0.90 M, but the enthalpy of complex formation decreased from -10.4 ± 0.3 to -15 ± 1 kJ/mol. Similar results were obtained with α-cyclodextrin.

Some of the results obtained in this work can be compared with previously reported values. Equilibrium constants for *p*-nitrophenol and *m*-nitrophenol with the cyclodextrins and substituted cyclodextrins are in general agreement with values determined by a thin-layer chromatographic technique.[17] Cramer et al.[6] determined equilibrium constants for *p*-nitrophenol and *p*-nitrophenolate (pH 11) complexes with α-cyclodextrin by UV spectroscopy. Interpolation of their results to 25 °C gives equilibrium constants about 15–30% greater than those reported in Table I but only slightly outside of the uncertainty limits of this work. Enthalpies of complexation calculated from the temperature dependence of their equilibrium constants are somewhat smaller than those

(13) Hirata, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1410.
(14) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978.
(15) Boehm, R. E.; Martire, D. E.; Armstrong, D. W. *Anal. Chem.* **1988**, *60*, 522.
(16) Bertrand, G. L. Unpublished data, this laboratory, 1987.
(17) Han, S. M.; Armstrong, D. W.; Purdie, N. Manuscript in preparation.

TABLE I: Calorimetric Results for Complexes of *p*-Nitrophenol and *m*-Nitrophenol with Cyclodextrins at 298.15 K[h]

	K, L/mol				
	this work	other studies	$\Delta G°$, kJ/mol	$\Delta H°$, kJ/mol	$\Delta S°$, J/mol·K
		A. *p*-Nitrophenol			
α-cyclodextrin	220 ± 20	438[a]	−13.4 ± 0.2	−25.8 ± 0.4	−42 ± 2
		293[b]			
		341[d]			
		260[e]			
(pH 11.1)	1800 ± 300	2290[b]	−18.6 ± 0.4	−40.9 ± 0.9	−75 ± 3
		670[f]			
(1 N NaOH)	135 ± 11	270[g]	−12.2 ± 0.2	−20.2 ± 0.8	−27 ± 3
β-cyclodextrin	350 ± 50	142[a]	−14.5 ± 0.4	−12.0 ± 0.6	8 ± 2
(pH 11.1)	570 ± 25		−15.7 ± 0.1	−15.5 ± 0.2	1 ± 1
heptakis(2,6-di-*O*-methyl)-β-cyclodextrin	380 ± 50	289[a]	−14.7 ± 0.3	−10.5 ± 0.5	14 ± 2
(pH 11.1)	1070 ± 140		−17.3 ± 0.3	−17.1 ± 0.3	1 ± 1
heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin	128 ± 2	126[g]	−12.0 ± 0.5	−13.0 ± 0.9	−3 ± 3
(pH 11.1)	284 ± 12		−14.0 ± 0.1	−30.9 ± 0.5	−57 ± 2
		B. *m*-Nitrophenol			
α-cyclodextrin	124 ± 5	105[a]	−12.0 ± 0.1	−28.4 ± 0.7	−55 ± 2
		54[d]			
(pH 11.1)	202 ± 3		−13.2 ± 0.1	−32.0 ± 0.3	−63 ± 1
β-cyclodextrin	274 ± 27	93[a]	−13.9 ± 0.2	−12.1 ± 0.5	6 ± 2
(pH 11.1)	117 ± 19		−11.8 ± 0.4	−6.7 ± 0.6	17 ± 2
heptakis(2,6-di-*O*-methyl)-β-cyclodextrin	300 ± 30	230[a]	−14.1 ± 0.3	−11.0 ± 0.6	10 ± 2
(pH 11.1)	85 ± 15		−11.0 ± 0.4	−11 ± 2	0 ± 6

[a] Reference 17. [b] Reference 6. [c] Reference 7. [d] Reference 8. [e] Reference 10 (pH 6). [f] Reference 10 (pH 10). [g] Reference 10. [h] Additional values: for *p*-NP + α-CD, K = 125 L/mol,[c] $\Delta H°$ = −30 ± 6 kJ,[c] $\Delta H°$ = −18 kJ[b], for *p*-NP⁻ + α-CD, $\Delta H°$ = −30 kJ;[b] for *p*-NP + β-CD, K = 1000 L/mol,[c] $\Delta H°$ = −44 ± 10 kJ;[c] for *p*-NP⁻ + α-CD–*p*-NPH ⇔ α-CD–*p*-NP⁻ + *p*-NPH, K = 7.2 (pH titration); and for *p*-NP⁻ + β-CD–*p*-NPH ⇌ β-CD–*p*-NP⁻ + *p*-NPH, K = 1.6 (pH titration).

TABLE II: Thermodynamic Parameters for Complexes of Para-Substituted Phenols with Cyclodextrins at 25 °C

		α-cyclodextrin			β-cyclodextrin		
para-subst	V,[a] mL/mol	K, L/mol	$\Delta H°$, kJ/mol	$\Delta S°$, J/mol·K	K, L/mol	$\Delta H°$, kJ/mol	$\Delta S°$, kJ/mol·K
hydroxy[b]	87.8	24 ± 5	−10 ± 2	−7 ± 7	113 ± 5	−17.1 ± 0.5	−18 ± 2
c	89.4	37 ± 4	−10.2 ± 0.8	2 ± 2	94 ± 3	−12.2 ± 0.2	4 ± 1
chloro	102.2	292 ± 6	−20.1 ● 0.2	−20 ± 1	410 ± 60	−11.9 ± 0.4	10 ± 2
nitro	102.7	200 ± 10	−27.1 ± 0.2	−47 ± 1	260 ± 30	−13.4 ± 0.6	1 ± 2
bromo	105.5	710 ± 10	−25.6 ± 0.2	−31 ± 1	860 ± 160	−12.2 ± 0.3	15 ± 2
methyl[d]	106.9	37 ± 3	−17.7 ± 0.7	−29 ± 2	250 ± 10	−12.5 ± 0.2	4 ± 1

[a] Molar volume of similarly substituted benzene (see text). [b] Hydroquinone. [c] Phenol. [d] *p*-Cresol.

determined calorimetrically in this work. Equilibrium constants for the *p*-nitrophenolate complex with α-cyclodextrin differ substantially from those determined by Inoue et al. using NMR,[10] but the same general trend is observed in the strong weakening of the complex on going from pH 11 to 1 N sodium hydroxide. Lewis and Hansen[7] determined equilibrium constants and enthalpies of complexation for phenol and *p*-nitrophenol with α-cyclodextrin by a calorimetric method. Our results agree with this work within the very large uncertainties they report. Our enthalpy for the complex of *p*-nitrophenol with β-cyclodextrin (−12.0 ± 0.6 kJ/mol) does not agree with the value reported in that work (−44 ± 10 kJ/mol), though our equilibrium constant (350 ± 50) is within the uncertainty range (log K = 3.0 ± 1.7) reported there. Buvari and Barcza[12] have determined equilibrium constants for complexes of β-cyclodextrin with phenol, *m*-nitrophenol, *p*-nitrophenol, and their anions by a spectrophotometric technique involving variation of pH. Our results are in general agreement, though that work involved several different buffers with no specification of ionic strength.

The effect of ionization on the equilibrium constants for complexes of the nitrophenols with cyclodextrins can be checked by an alternate means. The ratio of equilibrium constants for complexation of the anion relative to the molecule must be the same as the ratio of ionization constants of the bound molecule/ion relative to the free or uncomplexed species, since both ratios refer to the following equilibrium:

$$\text{D–(free)} + \text{HD (bound)} \Leftrightarrow \text{D–(bound)} + \text{HD (free)} \quad (6)$$

Ionization constants were determined by pH titrations of *p*-nitrophenol and *m*-nitrophenol in water and in excess cyclodextrin solutions. These ratios, corrected for incomplete complexation, were in excellent agreement with ratios of the equilibrium constants reported in Table I.

Discussion

This study was designed to provide a comparison of the thermodynamic parameters for the binding of phenols to cyclodextrins for a variety of conditions, including variation of the size and shape of the phenol, size and degree of methylation of the cyclodextrin, and the effects of pH and ionic strength.

For molecular species, we have found that binding constants with β-cyclodextrin are generally larger than those for α-cyclodextrin with the same substituted phenol, but the enthalpies of complex formation are much more negative for complexes with α-cyclodextrin than with β-cyclodextrin in most cases. Methylation of the hydroxyl groups of β-cyclodextrin has very little effect on the binding constants for *m*- and *p*-nitrophenols, but generally leads to less negative enthalpies of complex formation. Enthalpies of complex formation with α-cyclodextrin are much more sensitive to the size and shape of the phenolic guest molecule than are those with β-cyclodextrin.

These observations are compatible with the generally accepted idea of α-cyclodextrin complexes holding the phenolic molecule in the cavity with relatively large binding energy in one or two tightly bound configurations. Complexes with β-cyclodextrin, however, appear to be more loosely bound in the large cavity with somewhat lower binding energy, but several configurations of comparable energy, leading to a larger entropy of complexation. This compensation between entropic and enthalpic effect is most readily seen in terms of the following exchange reaction:

$$\text{RPh–α-CD(aq)} + \text{β-CD(aq)} \rightarrow \text{α-CD(aq)} + \text{RPh–β-CD(aq)} \quad (7)$$

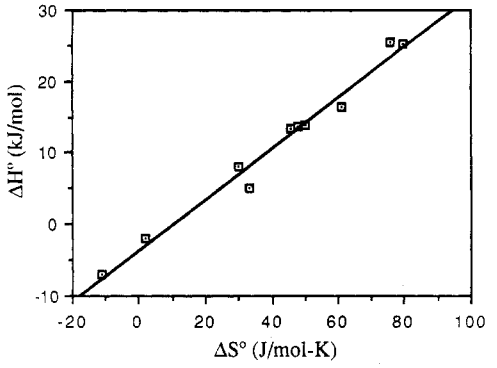

Figure 1. Enthalpy vs entropy of transfer of phenols from complex with α-cyclodextrin to β-cyclodextrin.

Thermodynamic parameters ($\Delta G°$, $\Delta H°$, $\Delta S°$) can be calculated for this reaction by differences of the values in Tables I and II for different substituents (R). This combination eliminates the effects of solvation of the free phenols in water, and the difference in solvation of the cyclodextrins is a fixed contribution for all of the substituted phenols. Values of $\Delta H°$ are plotted against $\Delta S°$ for this reaction in Figure 1. Included in this graph are the effects of ionic strength, ionization, and both meta and para substituents. This relationship is given by ΔH (kJ/mol) = $-3.6 + 0.36\Delta S$ (J/mol·K) with a standard deviation of 1.5 kJ/mol. Methylation of the hydroxyl groups of β-cyclodextrin leads progressively to complexes with lower binding energy but greater entropy. Values calculated for the transfer of the nitrophenols and their anions from α-cyclodextrin to methylated β-cyclodextrins also may be included in this correlation but with a bit more scatter.

While the phenolate ions show the same entropic–enthalpic compensation as molecular phenols in the transfer from α- to β-cyclodextrin, the ions show a marked difference in behavior in that equilibrium constants are larger for α-cyclodextrin complexes than for those with β-cyclodextrin. The reduced binding power of cyclodextrins in 1 N sodium hydroxide solution has been attributed to deprotonation of the cyclodextrin.[10] The equilibrium constants for the *p*-nitrophenolate complex with α-cyclodextrin at pH 11 and 1 N sodium hydroxide are compatible with an equilibrium constant of 16.5 L/mol[18] for the reaction

$$\alpha\text{-CD(aq)} + \text{OH}^-\text{(aq)} \Leftrightarrow \alpha\text{-CD}^-\text{(aq)} \qquad (8)$$

if the anionic form of the cyclodextrin (whether deprotonated or complexed with hydroxide ion) is assumed to be incapable of forming an inclusion complex.

The crystallographic structure[13] of the α-cyclodextrin complex with *p*-nitrophenol shows the phenolic hydroxyl group at the top of the cyclodextrin "basket" with the nitro group down inside the cavity. The guest molecule appears to be too large for complete immersion in the cavity. An NMR study of ring current effects on the aromatic protons of inclusion complexes of α-cyclodextrin with several para-substituted phenols[10] has confirmed this size effect. This suggests a possible correlation of thermodynamic properties of these inclusion complexes with the size of the guest molecules. Molar volumes have been calculated for pure liquids analogous to the phenols without the hydroxyl group, and these are listed in Table II. Thus, the molar volume of liquid benzene is listed for phenol, that of toluene for *p*-cresol, and that of phenol (extrapolated from higher temperatures) for hydroquinone. Enthalpies of formation of α-cyclodextrin complexes show a fairly smooth trend with volume, with the nitro and bromo derivatives showing the strongest interactions and the larger methyl derivative showing a reduced effect. Similar trends are seen for free energies and entropies of formation, but these are not so well defined.

A similar trend in free energy with size of the guest molecule is observed for the β-cyclodextrin complexes but not for enthalpies or entropies of formation. With the exception of hydroquinone, all of the β-cyclodextrin complexes have standard enthalpies of formation around −12 kJ/mol. The NMR study by Inoue et al.[10] of inclusion complexes of β-cyclodextrin and para-substituted phenols (hydroquinone was not included in that study) found the guest molecule completely penetrating the hydrophobic cavity of the cyclodextrin. In this case, the hydroxyl group and the para substituent of the phenol could both be located in hydrophilic environments, and undergo little change of environment on forming the inclusion complex. Only the hydrophobic aromatic ring undergoes a change from an aqueous environment to a nonpolar environment, and the energy of complex formation is then somewhat independent of the nature of the substituent. The different shapes, sizes, and polarities of the substituent groups could affect the number of allowable conformations of the guest molecule within the cavity and thus lead to entropic differences that would dominate the relative binding constants.

The hydroquinone complexes seem to differ somewhat from the other complexes. The enthalpy of formation of the complex with α-cyclodextrin is the weakest in this study, while the enthalpy and entropy of formation of the complex with β-cyclodextrin are the most negative of the phenols studied here. The hydroxyl group appears reluctant to enter the hydrophobic cavity of α-cyclodextrin, as evidenced by the preferred orientation of nitrophenol with the nitro group in the cavity and of *p*-hydroxybenzoic acid with the carboxylic acid group within the cavity.[10,13] The strong interaction with β-cyclodextrin is probably due to some preferred orientation of the hydroquinone molecule penetrating the cavity and forming strong hydrogen bonds with hydroxyl groups at both the top and bottom of the cavity.

Acknowledgment. Support of this work by the Department of Energy, Office of Basic Research (DE-FG02-88ER13819), is gratefully acknowledged.

Appendix

The primary data for these measurements are as follows: [D]* = initial concentration of donor solution in buret,; [A]* = initial concentration of acceptor solution in flask; W = weight of the acceptor solution in the flask; d = density of acceptor solution; DV = volume of donor solution added; and H/V = enthalpy change per milliliter of donor solution added.

The secondary data are as follows: [D]° = final formal concentration of donor in flask; [A]° = final formal concentration of acceptor in flask; $[D]° = (DV)[D]^*/(DV + W/d)$; $[A]° = [(W/d)[A]^*]/(DV + W/d)$; $(\Delta H_D)_{1or2}$ = enthalpy per mole of donor; $(\Delta H_D)_{1or2} = (H/V)_{1or2}/[D]^*$; $\Delta_{tr}H_D$ = enthalpy of transfer per mole of donor from water to acceptor solution at same [D]°; $\Delta_{tr}H_D = (\Delta H_D)_1 - (\Delta H_D)_2$; H/L = enthalpy of transfer per liter of solution; and $H/L = [D]°\Delta_{tr}H_D$. Subtraction of process II from process I at a fixed value of [D]° gives the following:

$$n_D°\text{D (aq, [D]°, } T) + n_A°\text{A (aq, [A]*, } T) \rightarrow \{n_A\text{A}, n_D\text{D}, n_C\text{C}\}\text{ (aq, [A]°, [D]°, } T)$$

The observed enthalpy change for this process is $n_D°\Delta_{tr}H_D$. In the ideal dilute solution approximation, all enthalpies of dilution are zero, and the enthalpy change for this process is assumed to be the product of the number of moles of complex formed and the standard enthalpy of formation of 1 mol of the complex ($n_C\Delta_{rx}H°$). The validity of this approximation was checked by measuring the enthalpy of transfer of hydroquinone from a blank solution at pH 4.1 and ionic strength 0.18 M to a similar solution containing maltose, which should produce an environment similar to cyclodextrin solutions but is not expected to form complexes. The enthalpy of transfer to 0.047 M maltose was -0.10 ± 0.05 kJ/mol, compared to −2.70 kJ/mol for the transfer to 0.015 M α-cyclodextrin with a comparable concentration of glucose units. The complex between hydroquinone and α-cyclodextrin gave the weakest thermal responses encountered in this study.

To simplify calculations, we assume a volume of 1 L for the final solution so that concentrations and numbers of moles become identical and the observed enthalpy is H/L. The ideal dilute solution approximation also assumes that all activity coefficients are unity, and the equilibrium constant takes the following form:

(18) Bertrand, G. L.; Li, W.; Armstrong, D. W. Manuscript in preparation.

$$K = [C]/[A][D] = [C]/([A]^\circ - [C])([D]^\circ - [C])$$

$$H/L = [C]\Delta_{rx}H^\circ$$

Measurements of H/L values for two or more values of $[A]^\circ$ and/or $[D]^\circ$ allows simultaneous solution for the "best" values of K and $\Delta_{rx}H^\circ$. Because of the finite concentrations of both components, the concentration of the complex is given by a quadratic equation:

$$[A]^\circ[D]^\circ - [C]\{[A]^\circ + [D]^\circ + 1/K\} + [C]^2 = 0$$

The squared term prevents simple solution of these equations by linear regression and is often approximated as zero. Combination of these equations gives

$$\{[A]^\circ[D]^\circ + [C]^2\}/\{H/L\} = 1/K\Delta_{rx}H^\circ + \{[A]^\circ + [D]^\circ\}/\Delta_{rx}H^\circ$$

If [C] can be approximated, this becomes a linear form

$$Y = b + mX$$

with

$$Y = \{[A]^\circ[D]^\circ + [C]^2\}/\{H/L\} \qquad X = [A]^\circ + [D]^\circ$$

for each data point. The approximate solution takes [C] = 0 in calculating values of Y. A reiterative program then performs a weighted linear regression minimizing the deviations in values of H/L. Approximate values are calculated from $K = m/b$ and $\Delta_{rx}H^\circ = 1/m$. This approximate value of K is used with the formal concentrations of donor and acceptor in the quadratic equation to calculate values for [C] and improved values of Y, leading to an improved value of K. This process is continued until successive values of K agree to within 0.01%, and this value of K and its statistical standard deviation are taken as "best" values, along with the corresponding values of $\Delta_{rx}H^\circ$ and its standard deviation. These calculations were performed on an Apple IIe microcomputer.

An alternate weighting procedure that minimizes deviations in the molar enthalpy of transfer was also considered. In most cases, the results of the two calculational procedures agreed to within the estimated uncertainties of either. However, calculations on different subsets of the elements of some of the data sets show that uncertainty estimates are somwhat more reliable when based on minimization of the deviations in the quantity H/L. Uncertainties calculated by conventional unweighted regression, which minimizes deviations in Y or the reciprocal of H/L, are less reliable than either of the weighted procedures.

Growth and Some Properties of Large Praseodymium Pentaphosphate Single Crystals

Lixia Li, Jiyang Wang,* Zhaohe Yang, Huizhu Jiang, and Yaogang Liu

Shandong University, Jinan, Shandong, People's Republic of China *(Received: July 19, 1988; In Final Form: March 23, 1989)*

By means of a high-temperature solution-seeded method, praseodymium pentaphosphate (PrPP) single crystals have been grown directly by using Pr_6O_{11} and H_3PO_4 as raw materials. The dimension of a PrPP single crystal even reaches as large as 72 × 22 × 13 mm. Its morphology, XRD, and specific heat data are all determined. In addition, the Raman spectra of PrPP, LaP_5O_{14} (LaPP), and $Pr_xLa_{1-x}P_5O_{14}$ (PrLaPP) crystal series are also reported in this paper. The phonon soft modes of PrPP crystal corresponding to A_g–B_{2g} and B_g–B_{3g} have been observed in two geometrical arrangements, $Z(YZ)X$ and $Z(XZ)Y$, respectively. It is shown that the frequencies, intensities, and peak shapes change evidently with temperature. On the basis of the changes of the soft modes with the temperature, the temperature at which the C_{2h}–D_{2h} ferroelastic phase transition of PrPP crystal takes place can be deduced. Accordingly, the ferroelastic phase-transition temperature of PrPP crystal is obtained, i.e., 137 ± 1 °C.

Praseodymium pentaphosphate (PrP_5O_{14}, abbreviated as PrPP), like neodymium pentaphosphate, is a kind of stoichiometric self-activated laser crystal. Since it can realize laser output at 637 and 717 nm, PrPP is expected to be a laser operation material having prosperous applications.

By means of a high-temperature solution-seeded method, PrPP and $Pr_xP_5O_{14}$ (abbreviated as PrLaPP when x = 0–1 or LaPP when x = 0) crystals have been grown. Large PrPP crystals (up to 72 × 22 × 12 mm) with good optical quality are grown directly, with use of Pr_6O_{11} and H_3PO_4 as raw materials, which is different from that reported in ref 1. The crux is to keep the solution under high temperature for a long enough time to enable the Pr_6O_{11} to dissolve and change into Pr^{3+}. The reactions are as follows:

$$5H_3PO_4 \overset{450\ ^\circ C}{\rightleftharpoons} H_3P_5O_{14} + 6H_2O$$

$$Pr_6O_{11} + 6H_3P_5O_{14} = 6PrP_5O_{14} + 9H_2O + O_2$$

During the growth, a special water partial pressure should be maintained in the reactor. Otherwise, only small rhombic crystal plates are obtained, as reported previously.[1]

The morphology of PrPP crystal is determined with a double-ring goniometer. The ideal form of PrPP is shown in Figure 1. It belongs to a monoclinic system; the point group is C_{2h} ($2/m$), and it consists of 46 crystal facets. Among them, the (010) face is a complete cleavage face and (001) is an incomplete cleavage face.

X-ray powder diffraction data (XRD) obtained from PrPP and LaPP crystals are collected in a D/max-ra X-ray diffractometer and summarized in Table I.

The compositions of $Pr_xLa_{1-x}P_5O_{14}$ analyzed by using an X-ray microprobe are x = 1, 0.9, 0.8, ..., 0.1, 0. It is shown that the compositions of the crystals coincide with the original ratio of raw materials used in crystal growth.

The specific heats of PrPP, LaPP, and several $Pr_xLa_{1-x}P_5O_{14}$ (x = 0.1, 0.3, 0.5, 0.7, and 0.9) crystals at different temperatures have been measured by means of DSC-2C differential scanning calorimeter (produced by Perkin-Elmer). The temperature was varied from 290 to 525 K and the temperature-raising rate was 10 K/min. All experiments were performed under normal pressure. The samples used are all small pieces of crystal (each about 45 mg) with regular shapes and are flat enough to be contacted with the sample plates tightly. Before the measurements, the calorimeter was calibrated with a standard metal—indium. The melting point and melting heat of indium are 429.78 K and

(1) Borkowski, B.; Grzesiak, E.; Kaczmarek, F.; et al. *J. Cryst. Growth* **1978**, *44*, 320.

0022-3654/89/2093-6867$01.50/0