Electrostatically-Induced Inclusion of Anions in Cyclodextrin Monolayers on Electrodes

Richard V. Chamberlain II, Katarzyna Slowinska, and Marcin Majda*

Department of Chemistry, University of California at Berkeley, Berkeley, California 94720-1460

Philippe Bühlmann, Hiroshi Aoki, and Yoshio Umezawa*

Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received June 24, 1999. In Final Form: September 28, 1999

Oxidative mercury−thiolate bond formation accounts for the assembly of densely packed monolayers of per-2,3-methylated per-6-thiolated α-, β-, and γ-cyclodextrins on the hanging mercury drop electrode. Inclusion of inorganic ions and uncharged hydrophobic guests into these monolayers was investigated by capacitance measurements. In the range of potentials where the electrode is positively charged, the interfacial capacitance depends on the type of electrolyte anions and on the applied potential. This can be explained with electrostatic double-layer forces. Whereas the smaller and less well solvated anions Cl^-, NO_3^-, and ClO_4^- are included in the cyclodextrin cavities of these monolayers, the larger and more strongly solvated anions F^-, SO_4^{2-}, and $H_2PO_4^-$ are excluded. Anion inclusion constants can be obtained from the dependence of the interfacial capacitance on the anion concentration. The potential dependence of these inclusion constants shows that the nonelectrostatic contribution to the driving force for NO_3^- inclusion is negligibly small. Competitive binding of hydrophobic guest molecules decreases the interfacial capacitance. Fitting Langmuir isotherms to the plots of the interfacial capacitance as a function of adamantanol concentration yielded the binding constants 1.0×10^4 and 2.6×10^4 M^{-1} for the β- and γ-cyclodextrin monolayers, respectively. Binding of adamantanol to α-cyclodextrin monolayers could not be observed, apparently because this guest is too large for the internal cavity of the α-cyclodextrin receptor. In contrast, 1-hexanol binds to α-cyclodextrin monolayers with the binding constant 8.9×10^4 M^{-1}. This shows that changes in the capacitance can serve as a general signal transduction mode to monitor interactions between cyclodextrin monolayers and charged or neutral guests. Also, the extension of these types of measurements into solid electrodes and the application to other guest-selective host monolayers open the possibility of designing a novel type of electrochemical sensors for electroinactive analytes.

Introduction

Molecular recognition of analytes by host−guest chemistry is a promising approach to chemical sensing. In this report, we describe the recognition of anionic guests at cyclodextrin monolayers, as observed by the measurement of interfacial capacitances. Cyclodextrins are tube-shaped cyclic oligosaccharides featuring largely hydrophobic internal cavities of variable size. They were the subject of numerous investigations, including their use for the preparation of electrode surface films.[1−7] Because of their fairly rigid structure, they found particular interest as mimics of biological ion channels. Also, there is a wealth of information on binding of guest molecules to cyclodextrins in homogeneous solution.[8] Interestingly, formation of host−guest inclusion complexes can be used to gate cyclodextrin channels. This is of particular interest because only a few of the biomimetic intramolecular channels studied so far[1,6,7,9,10] can be gated by recognition of chemical species.[1,6] The first example was reported by Umezawa et al., who formed monolayers of an amphiphilic cyclodextrin derivative at the air−water interface in a Langmuir−Blodgett trough and measured cyclic voltammograms upon contacting the monolayers in situ with a planar electrode. The presence of cyclodextrin guests in the aqueous phase decreased *p*-quinone reduction currents, apparently by blocking the intramolecular channels of the cyclodextrins. Osa et al. later obtained similar results with gold electrodes modified with self-assembled monolayers of a cyclodextrin derivative with two thiol groups per molecule.[6] Not a channel function but competitive adsorption of electroactive and electroinactive markers was reported for three other types of electrodes modified with cyclodextrin monolayers.[3,5,7]

While much is known about interactions between organic guests and cyclodextrins,[8] interactions between inorganic ions and cyclodextrins have drawn much less

(1) Odashima, K.; Kotato, M.; Sugawara, M.; Umezawa, Y. *Anal. Chem.* **1993**, *65*, 927.

(2) Henke, C.; Steinem, C.; Janshoff, A.; Steffan, G.; Luftmann, H.; Sieber, M.; Galla, H.-J. *Anal. Chem.* **1996**, *68*, 3158. Lahav, M.; Ranjit, K. T.; Katz, E.; Willner, I. *Isr. J. Chem.* **1997**, *37*, 185. Ju, H.; Leech, D. *Langmuir* **1998**, *14*, 300. Wang, Y.; Kaifer, A. E. *J. Phys. Chem. B* **1998**, *102*, 9922. Stine, K. J.; Andrauskas, D. M.; Khan, A. R.; Forgo, P.; D'Souza, V. T. *J. Electroanal. Chem.* **1999**, *465*, 209. Hromadova, M.; de Levie, R. *J. Electroanal. Chem.* **1999**, *465*, 51.

(3) Rojas, M. T.; Königer, R.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1995**, *117*, 336.

(4) Nelles, G.; Weisser, M.; Back, R.; Wohlfart, P.; Wenz, G.; Mittler-Neher, S. *J. Am. Chem. Soc.* **1996**, *118*, 5039.

(5) Maeda, Y.; Fukuda, T.; Yamamoto, H.; Kitano, H. *Langmuir* **1997**, *13*, 4187.

(6) He, P.; Ye, J.; Fang, Y.; Suzuki, I.; Osa, T. *Anal. Chim. Acta* **1997**, *337*, 217−223. He, P.; Ye, J.; Fang, Y.; Suzuki, I.; Osa, T. *Electroanalysis* **1997**, *9*, 68.

(7) Weisser, M.; Nelles, G.; Wenz, G.; Mittler-Neher, S. *Sens. Actuators, B* **1997**, *38*−*39*, 58.

(8) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978. Szejtli, J. *Cyclodextrin Technology*; Kluwer: Dordrecht, 1988. Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325. Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875. Lipkowitz, K. B. *Chem. Rev.* **1998**, *98*, 1829.

10.1021/la990826i CCC: $19.00
Published on Web 11/16/1999

attention. Whereas the hydrophobic interactions are the major driving force in size-selective binding of hydrophobic molecules, we show in this report that electrostatic double-layer forces are primarily responsible for selective inclusion of small hydrophilic anions to cyclodextrin monolayers on hanging mercury drop electrodes (HMDEs). We demonstrate in this work that inclusion of such anions into α-, β-, and γ-cyclodextrins results in substantial increases of the interfacial capacitance. Conversely, competitive binding of hydrophobic molecules results in anion expulsion and decreases the interfacial capacitance. These results show that changes of the capacitance of the CD*-modified interface can serve as a general signal transduction mode and can be used to monitor quantitatively interactions between host monolayers and charged or neutral guests. Also, this shows the possibility of designing a novel class of electrochemical sensors on the basis of analyte recognition at host monolayers.

Measurements of interfacial capacitances were used previously to monitor inclusion of ionic guests to interfacial receptor monolayers.[11,12] Smith and White developed a quantitative model for the interfacial capacitance of host monolayers, taking into account the effect of the applied potential on inclusion of ionic guests. Also, Ghadiri et al. used impedance spectroscopy to demonstrate the size-selective permeabilities of membranes incorporating intramolecular channels formed by cyclic peptides.[10] However, capacitance measurements have not been reported so far to describe quantitatively complexation of uncharged guests by receptor sites in monolayers. Interestingly, host−guest interactions in Langmuir−Blodgett or self-assembled monolayers exposed to liquid samples have only rarely been investigated quantitatively. Usually, this involved the determination of adsorbed electroactive species.[3,5,6,13,14] Therefore, it is not surprising that the binding constants that would allow the direct comparison of the stabilities of cyclodextrin−guest complexes in solution and in cyclodextrin monolayers do not appear to be known.

Self-assembled monolayers (SAMs) of cyclodextrin mono- or oligothiol derivatives on gold electrodes were reported to be rather strongly disordered. For example, Kaifer et al. reported that monolayers of a β-cyclodextrinheptathiol on gold electrodes did not efficiently inhibit the electron transfer of the redox couples $[Ru(NH_3)_6]^{3+/2+}$ and $[Fe(CN)_6]^{3-/4-}$.[3] The number of intermolecular voids in CD SAMs could only be diminished either by backfilling such voids with alkanethiols[5,14] or by using cyclodextrin derivatives that are attached to the underlying gold substrate by long alkyl chains.[4,15] A limited lateral mobility of the cyclodextrin receptors on gold electrodes and the surface roughness of Au electrodes were suspected to explain the unsatisfactorily high extent of disorder in such SAMs.[4,15] This seems particularly so for cyclodextrin derivatives with more than one thiol group per molecule.

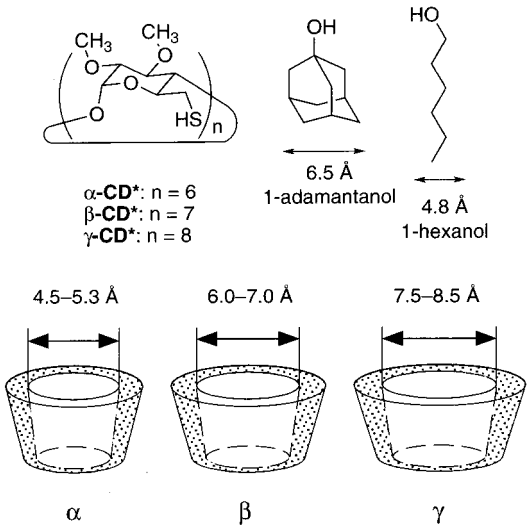

Figure 1. Structure formulas and dimensions of α-, β-, and γ-CD* and their guests 1-adamantanol and 1-hexanol. The ranges for the diameters of the internal cyclodextrin cavities reflect the tapered shape of these receptor compounds. The CD*s are methoxy-substituted on the wider upper rims, which upon self-assembly face the electrolyte solution.

Therefore, in this study, cyclodextrin monolayers were formed mainly on mercury electrodes.[16,17] Due to its liquid nature at room temperature, the hanging mercury drop electrode has an atomically flat surface conducive to the formation of highly ordered monolayers. Furthermore, formation of mercuric thiolate bonds does not restrict the lateral mobility of bound molecules on Hg. As shown below, this results in significantly higher packing densities relative to those for self-assembly on Au.

Experimental Section

Reagents. Mercury (Bethlehem Apparatus Co., Hellertown, PA, triply distilled, or Aldrich Chemical Co., Milwaukee, WI, >99.9995%), ethanol (reagent grade, Fisher Scientific, Fair Lawn, NJ, or Nacalai Tesque Inc., Kyoto, Japan), 1-adamantanol (Wako Pure Chemicals, Osaka, Japan), 1-hexanol (Tokyo Kasei Kogyo, Tokyo, Japan), phosphoric acid (Fisher Scientific), and KOH (Wako or Fisher Scientific) were used as received. Phosphate buffer was prepared by adjusting the pH of a KH_2PO_4 or a phosphoric acid solution with KOH, unless mentioned otherwise. All electrolyte salts (Wako, Aldrich, or Fisher Scientific) were of the highest grade commercially available. Deionized and charcoal-treated water prepared with Milli-Q type I (Millipore, Bedford, MA) or house-distilled water passed through a four-cartridge Nanopure II (Barnstead, Boston, MA) reagent grade water system was used for all experiments. The final resistivity of the water was in the range 17.6−18.3 MΩ cm.

Syntheses. Per-(6-deoxy-6-bromo) derivatives of β- and γ-cyclodextrin were obtained from the native cyclodextrins by bromination with triphenylphosphine/Br_2.[18] Per-(6-deoxy-6-iodo)-α-cyclodextrin was synthesized analogously by iodination with I_2.[18] Subsequent reaction with benzylthiol yielded hexa-, hepta-, and octa-*S*-benzyl ethers. Upon permethylation of the secondary hydroxy groups, the *S*-benzyl thioethers were cleaved with Na/NH_3 to give α-, β-, and γ-CD* (see Figure 1). For a detailed synthesis description and product characterization, see the Supporting Information.

(9) Fyles, T. M.; van Straaten-Nijenhuis, W. F. In *Comprehensive Supramolecular Chemistry*; Reinhoudt, D. N., Ed.; Pergamon: Oxford, 1996; Vol. 10, p 53. Akerfeldt, K. S.; Kienker, P. K.; Lear, J. D.; DeGrado, W. F. In *Comprehensive Supramolecular Chemistry*; Reinhoudt, D. N., Ed.; Pergamon: Oxford, 1996; Vol. 10, p 659.

(10) Motesharei, K.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1997**, *119*, 11306.

(11) Smith, C. P.; White, H. S. *Langmuir* **1993**, *9*, 1.

(12) Gafni, Y.; Weizman, H.; Libman, J.; Shanzer, A.; Rubinstein, I. *Chem. Eur. J.* **1996**, *2*, 759.

(13) Godinez, L. A.; Patel, S.; Criss, C. M.; Kaifer, A. E. *J. Phys. Chem.* **1995**, *99*, 17449. Rojas, M. T.; Kaifer, A. E. *J. Am. Chem. Soc.* **1995**, *117*, 5883.

(14) Lee, J.-Y.; Park, S.-M. *J. Phys. Chem. B* **1998,** *102*, 9940.

(15) Weisser, M.; Nelles, G.; Wohlfart, P.; Wenz, G.; Mittler-Neher, S. *J. Phys. Chem.* **1996**, *100*, 17893.

(16) Demoz, A.; Harrison, D. J. *Langmuir* **1993**, *9*, 1046. Slowinski, K.; Chamberlain, R. V., II; Bilewicz, R.; Majda, M. *J. Am. Chem. Soc.* **1996**, *118*, 4709. Stevenson, K. J.; Mitchell, M.; White, H. S. *J. Phys Chem. B* **1998**, *102*, 1235.

(17) Slowinski, K.; Chamberlain, R. V., II; Miller, C. J.; Majda, M. *J. Am. Chem. Soc.* **1997**, *119*, 11910.

(18) Gadelle, A.; Defaye, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 78−80. Gorin, B. I.; Riopelle, R. J.; Thatcher, G. R. J. *Tetrahedron Lett.* **1996**, *37*, 4647.

Hanging Mercury Drop Electrodes (HMDEs). Kemula−Kublik type HMDEs with silanized glass capillaries were constructed as reported previously.[17] Cyclodextrin monolayers were prepared by exposure of the hanging mercury drop for 30 s to a 0.1 mM ethanol solution of the cyclodextrin, followed by rinsing with ethanol for 10 s and with water for 5 s. The electrochemical cell was then raised to submerge the HMDE into the electrolyte solution, which had been purged before with argon for at least 15 min.

Gold Electrodes. Glass slides were cleaned with soap water, water, and 2-propanol, boiled for 10 min in 2-propanol−chloroform (1:1), dried, and put into a Veeco 7700 evaporator (Veeco, Plainview, NY). A 10 nm chromium layer and a 80 nm Au layer were deposited onto the glass slides using an aluminum mask. The geometric area of the electrodes was 0.20 cm^2. The Au surfaces were then washed with $K_2Cr_2O_5/H_2SO_4$, water, HF, and water. Monolayers of β-CD* were prepared by soaking the electrodes for 2 h at 50 °C in a 0.1 mM solution of β-CD* in ethanol, followed by rinsing with water. Reductive desorption to determine the surface concentration of β-CD* was performed in 0.5 M KOH at a potential scan speed of 100 mV/s.[3] Attempts to backfill intermolecular voids between β-CD* molecules were performed by dipping β-CD*-modified electrodes into water−ethanol mixtures (1:10) containing 2 mM 1-adamantanol and 0.5 mM 1-octanethiol.

Electrochemical Measurements. Electrochemical measurements were performed at 20 °C with a BAS 50 or BAS 100 electrochemical analyzer (West Lafayette, IN). All potentials are reported versus the saturated calomel reference electrode (SCE). A spiral platinum wire was used as the auxiliary electrode. The capacitance measurements were performed using AC voltammetry or fast scan cyclic voltammetry. All capacitance data represent averages and standard deviations of at least three independent measurements. Binding constants are reported with confidence intervals for the 95% level ($CI_{95\%}$).

Surface Pressure−Molecular Area (π−*A*) Isotherms. Cyclodextrin monolayers at the air−water interface were prepared on pure water at 21 °C. π−*A* isotherms were recorded with a KSV Model 2200 system equipped with a Wilhelmy type surface pressure balance and Whatman #1 filter paper as a Wilhelmy plate.

Results and Discussion

Formation of Cyclodextrin Monolayers on Mercury Electrodes. A number of cyclodextrin derivatives with thiol substituents have been reported recently.[1,3−7,14,15] Several of them have alkyl chain substituents that may play a role in binding of guest molecules. We tried to avoid this and wanted to be able to associate observed guest binding predominantly with the properties of the cyclodextrin cavity. Three derivatives of α-, β-, and γ-cyclodextrin (α-CD*, β-CD*, and γ-CD*) with perthiolated primary and permethoxylated secondary hydroxy groups were synthesized for this purpose. As shown in Figure 1, the thiol groups in each compound are directly bound to the lower rim of the cyclodextrin torus.

Monolayers of these cyclodextrins can be formed on mercury by formation of mercury−thiolate bonds, similarly to the formation of alkanethiolate films.[16,17] In the latter case, oxidative binding involving one electron per thiol was used, in coulometric experiments, to confirm monolayer formation and to determine the alkanethiolate surface coverage.[17] Likewise, brief exposure of a mercury electrode to a 0.1 mM ethanol solution of α-CD*, β-CD*, or γ-CD* was sufficient for complete monolayer formation. Voltammetric experiments with the CD*-modified HMDEs in cyclodextrin-free aqueous phosphate buffer of pH 6.4 yielded for each CD* a stable and reversible set of anodic/cathodic surface peaks. As shown in Figure 2, these peaks are centered around −0.6 V versus SCE. As indicated by the linear pH dependence of the formal potential with the slope 58 mV/pH for the β-CD* cyclodextrin monolayers,

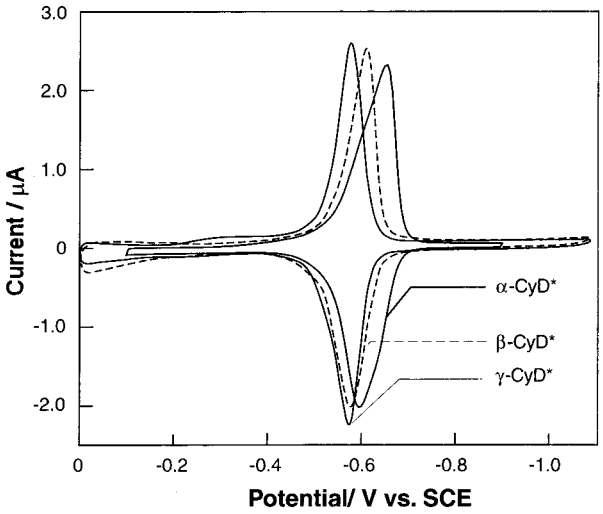

Figure 2. Cyclic voltammograms of α-, β-, and γ-CD*-modified Hg electrodes in 0.1 M phosphate buffer (pH = 6.4).

these peaks correspond to reversible oxidative coupling of the cyclodextrins to mercury by mercury−thiolate bond formation.

$$CD^*(S-Hg)_n + nH^+ + ne^- \overset{n = 6,\ 7,\ \text{or}\ 8}{\rightleftharpoons} CD^*(SH)_n + nHg^0$$

Interestingly, at pH 6.4, prolonged potential scanning in a wide potential window is possible without loss of surface coverage due to insolubility of these per-(2,3-methoxy-6-thio)-CD derivatives in aqueous solution. Only scanning the potential down to below −1.6 V leads to loss of the monolayer. The reversible character of the voltammetric peaks in prolonged voltammetric cycling shows that the water-insoluble cyclodextrin molecules remain physisorbed on the electrode surface even after the mercury−thiolate bonds are reductively broken. Furthermore, the lack of any additional voltammetric activity between 0.0 and −1.6 V suggests that the adsorbed cyclodextrins do not reorient upon mercury−thiolate bond reduction. Such reorientation would result in sharp pseudocapacitance peaks.[19]

Integration of the voltammetric reduction currents gave charges of 59 ± 2, 56 ± 2, and 53 ± 2 $\mu C/cm^2$ for α-CD*, β-CD*, and γ-CD*, respectively. Knowing that this redox activity results from the reductive breaking of the six, seven, or eight mercury−thiolate bonds, respectively, it follows that these charges correspond to the surface coverages 1.0×10^{-10}, 8.3×10^{-11}, and 6.8×10^{-11} mol/cm^2. This allows us to determine the mean molecular areas of these cyclodextrins as 164, 201, and 243 $Å^2$/molecule, respectively. As shown in Figure 3 for β-CD*, the voltammetrically determined mean molecular areas of β-CD* and γ-CD* in monolayers on mercury agree within 5% with the mean molecular areas for monolayers of these compounds at the air−water interface at the lateral pressure 4.0 mN/m. An analogous comparison for α-CD* is not possible because this compound does not form stable monolayers at the air−water interface. However, the value 164 $Å^2$/molecule agrees well with the value 167 $Å^2$/molecule, which is obtained from the crystal structure of nonderivatized α-cyclodextrin. These data show that self-assembly of β-CD* and γ-CD* on mercury results in formation of closely packed monolayers similar to those that can be obtained at the air−water interface.

(19) De Levie, R. *Chem. Rev.* **1988**, *88*, 599.

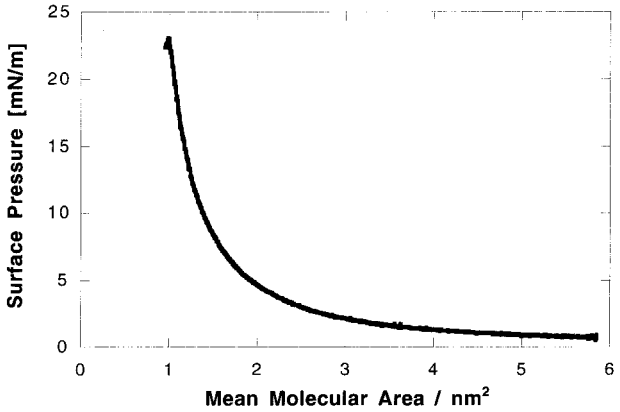

Figure 3. Surface pressure−molecular area (π−A) isotherm of a β-CD* monolayer on water as a subphase. Measured at 21 °C.

Table 1. Effect of Anions on the Capacitance of CD*-Modified HMDEs at −0.30 and −1.0 V versus SCE[a]

	capacitance at −0.30 V (μF/cm^2)			capacitance at −1.00 V (μF/cm^2)	
anion	α-CD*	β-CD*	γ-CD*	β-CD*	γ-CD*
NO_3^- [b]	16.0 ± 0.4	15.1 ± 0.4	15.2 ± 0.2	8.0 ± 0.2	9.0 ± 0.1
ClO_4^- [c]	14.1 ± 0.4	14.4 ± 0.3	15.1 ± 0.4	7.8 ± 0.2	8.7 ± 0.2
Cl^- [a]	30.7 ± 0.3	29.4 ± 1.7	27.8 ± 1.1	8.1 ± 0.3	9.3 ± 0.1
F^- [b,d]	10.2 ± 0.2	10.1 ± 0.5	10.0 ± 0.2	7.6 ± 0.3	8.5 ± 0.1
$H_2PO_4^-$ [b]	10.2 ± 0.3	9.6 ± 0.3	10.3 ± 0.2	7.4 ± 0.2	8.5 ± 0.3
SO_4^{2-} [c]	9.8 ± 0.3	9.4 ± 0.9	10.0 ± 0.1	7.4 ± 0.2	8.4 ± 0.1

[a] All solutions were prepared from potassium salts and contained 0.1 M phosphate buffer (pH = 6.4) unless noted otherwise. [b] 0.5 M. [c] 0.1 M. [d] Used as Na^+ salt.

Inclusion of Inorganic Anions into Cyclodextrin Monolayers. Interestingly, the cyclic voltammograms of the CD*-modified Hg electrodes indicated that the interfacial capacitance in the region negative of the main voltammetric signal was significantly smaller than its value in the potential region positive of the mercury−thiolate signal. This was surprising because the capacitance of an electrode covered with an adsorbent monolayer of a constant thickness usually does not depend significantly on the applied potential.[19] Subsequently, we measured the interfacial capacitance of CD*-modified Hg electrodes in various electrolyte solutions (Table 1). We found that the interfacial capacitance in the potential region positive of the mercury−thiolate signal depended strongly on the type of anion in the supporting electrolyte. We show in the following that these findings can be explained by electrostatically driven inclusion of ions into the cyclodextrin cavities. The selectivity of anion inclusion positive of the mercury−thiolate signal can be explained by the charge, hydrophilicity, and size of the hydrated ions. Furthermore, we show for nitrate that the driving forces for inclusion into these cyclodextrin monolayers are predominantly of an electrostatic nature.

The dependence of the interfacial capacitance on the composition of the supporting electrolyte was investigated in the potential regions in which the electrode surface is positively and negatively charged. The position of the potential of zero charge E_{pzc}, that is, the potential at which the CD*-modified mercury carries no excess charge, can only be approximated because E_{pzc} falls in the region of the mercury−thiolate signal. However, knowing that specific adsorption shifts E_{pzc} to more negative potentials and that in the absence of specific adsorption E_{pzc} is close to −0.47 V versus SCE,[20] it follows for the CD*-modified electrodes that $E_{pzc} < -0.47$ V. Considering that the reductive desorption of the CD* thiolates results in peaks

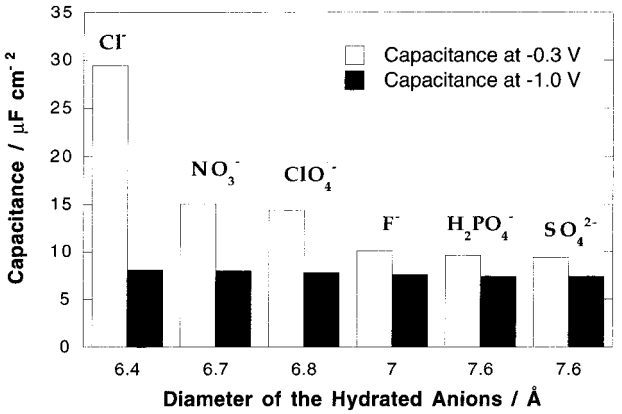

Figure 4. Dependence of the interfacial capacitance of β-CD*-modified Hg electrodes on the hydrated diameter of anions of a 0.5 M supporting electrolyte (with 0.1 M pH = 6.4 phosphate buffer) as measured at −0.30 V and −1.0 V versus SCE.

near −0.6 V versus SCE, it can be further concluded that E_{pzc} for all three types of monolayers is probably close to −0.65 V.

At −0.3 V, where the electrode surface is positively charged, the type of anions in the supporting electrolyte strongly affects the interfacial capacitance. Figure 4 and Table 1 show that the six anions NO_3^-, ClO_4^-, Cl^-, F^-, $H_2PO_4^-$, and SO_4^{2-} can be divided into two categories. Relative to the latter three, NO_3^-, ClO_4^-, and Cl^- have somewhat smaller hydrated diameters.[21,22] They appear to be drawn into the cyclodextrin cavities by the electrostatic forces in the electrical double-layer. This is reflected in significantly larger interfacial capacitances than those observed for the other three anions. A particularly high capacitance observed in the case of chloride ions is likely due to their specific adsorption on Hg,[20] which provides for an additional driving force for inclusion of Cl^- into the CD* cavities. The other three anions, F^-, $H_2PO_4^-$, and SO_4^{2-}, form a second category. They seem to be too large to be electrostatically drawn into CD* cavities. Therefore, they do not affect the interfacial capacitance (ca. 10.0 μF/cm^2) of the CD*-coated Hg−solution interface. Their higher extent of hydration relative to those of the first three anions is an important factor, as is discussed below. At −1.0 V, where the electrode is negatively charged, all six anions are electrostatically repelled. At this potential, the interfacial capacitance is constant and almost identical to that measured at −0.3 V in the electrolyte solutions containing the excluded anions F^-, $H_2PO_4^-$, or SO_4^{2-}.

The origin of the apparent selectivities of anion inclusion is of special interest. The cavities of the cyclodextrin derivatives used in our studies are tapered cylinders in shape. Using CPK models, we estimated their diameters to be 4.5−5.3, 6.0−7.0, and 7.5−8.5 Å for α-, β-, and γ-CD*, respectively. The dehydrated anions are all small enough to fit into the cavities of the three cyclodextrins. Therefore, inclusion of the dehydrated anions cannot explain the observed selectivity. The comparison of the hydrated diameters of the six anions (see Figure 4)[22] with the cavity diameter of β-CD* suggests that size exclusion could perhaps explain the capacitance data. However, despite its nominally large size, γ-cyclodextrin also does not allow

(20) Grahame, D. C. *Chem. Rev.* **1947**, *41*, 441.
(21) Marcus, Y. *Chem. Rev.* **1988**, *88*, 1475. Marcus, Y. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 713.
(22) The diameters of the hydrated ions were estimated from the values of the limiting equivalent ionic conductance (*Lange's Handbook of Chemistry*, 14th ed.; Dean, J. A., Ed.; McGraw Hill: New York, 1992) according to the method of Nightingale: Nightingale, E. R., Jr. *J. Phys. Chem.* **1959**, *63*, 1381.

inclusion of the anions F^-, $H_2PO_4^-$, and SO_4^{2-}, all of which have hydrated diameters smaller than or comparable to the size of the γ-cyclodextrin cavity (see Table 1). This points to the difficulty in estimating meaningful radii of hydrated anions. In view of this discussion, we postulate that the free energy required to extract the anions from the aqueous medium appears to be the decisive barrier that results in the exclusion of F^-, $H_2PO_4^-$, and SO_4^{2-}.

This interpretation is supported by similar findings on the interaction between inorganic anions and nonderivatized cyclodextrins in homogeneous aqueous solution. For α- and β-cyclodextrin there is a general trend to higher complex stabilities with the decreasing free energy of hydration ΔG_{hydr} of the anions.[23] (For γ-cyclodextrin sufficient data are not available.) The anions F^-, $H_2PO_4^-$, HPO_4^{2-}, SO_4^{2-}, and Cl^- are strongly hydrated ($\Delta G_{hydr} \leq -340$ kJ/mol) and do not bind to α- and β-cyclodextrin significantly (binding constants $K < 3\ M^{-1}$).[24−27] Also, NO_3^- ($\Delta G_{hydr} = -300$ kJ/mol) only weakly binds to α- and β-cyclodextrin ($K = 1-3$ and $0.2-5.5\ M^{-1}$, respectively).[24,27,28] Only the less hydrated ClO_4^- ($\Delta G_{hydr} = -205$ kJ/mol) binds significantly to α- and β-cyclodextrin ($K = 16.9-66$ and $9.0-16.7\ M^{-1}$, respectively).[26,29] Furthermore, a recent ^{1}H NMR spectroscopic study of complexes between inorganic anions and nonderivatized α-, β-, and γ-cyclodextrins in D_2O bulk solution[28] showed that neither $H_2PO_4^-$, HPO_4^{2-}, nor SO_4^{2-} binds to these cyclodextrins. On the other hand, weak binding of the hydrophobic anions ClO_4^- and SCN^- by inclusion of these anions into the cyclodextrin cavity was confirmed by large downfield shifts of the C(5)−H protons, which are located in the cavity of these cyclodextrins.[28]

It is interesting to compare the selectivity of inclusion into the internal cyclodextrin channels as observed in this study with the permeability of anion channels. While many artificial ion channels for cations have been reported in the literature, artificial ion channels for anions[10,30] are very few and do not allow us to discuss anion selectivities. On the other hand, anion selectivities were reported for a number of biological anion channels. While the electrostatic interactions between the anions and the cationic groups within channels seem to cause occasionally some deviations,[31] typical permeability selectivities for anions with radii smaller than a threshold value characteristic for each type of channel protein fall into the sequence of their hydrophilicities. Only anions with a larger radius than the channel are discriminated.[32] The selectivities of typical biological ion channels thus resemble that of the anion inclusion into the cyclodextrin channels described here.

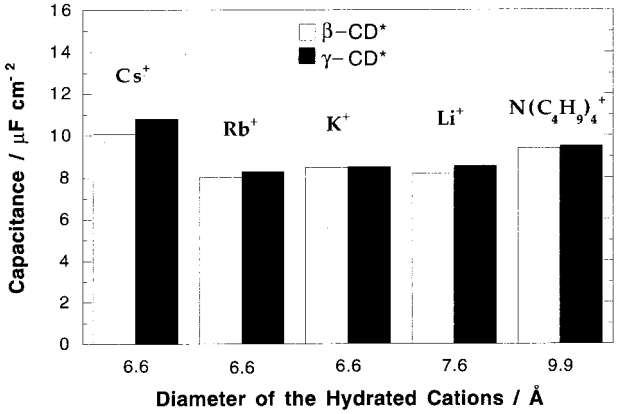

Figure 5. Dependence of the interfacial capacitance of β-CD*- and γ-CD*-modified Hg electrodes on the hydrated diameter of the cations of the supporting electrolyte (with 0.1 M phosphate buffer; pH = 6.3) as measured at −1.25 V versus SCE (Rb^+, Cs^+, 0.1 M; Li^+, K^+, $(C_4H_9)_4^+$, 0.5 M; all used as hydroxide salts and neutralized with phosphoric acid to pH 6.3).

Given this evidence for anion inclusion at potentials positive of E_{pzc}, we wondered whether similar evidence could also be obtained for cation inclusion at potentials negative of E_{pzc}. Indeed, capacitance measurements also provided some evidence for cation inclusion into CD* monolayers in the range of potentials in which the electrode is negatively charged (see Figure 5). On one hand, when Li^+, K^+, and Rb^+ solutions are used, the interfacial capacitance is not affected by the type of cation. On the other hand, there is a small increase in the capacitance for tetrabutylammonium and a larger increase for Cs^+. By analogy to the case of the anions, this result (Figure 5) can be interpreted in terms of the size and hydration energies of these cations. While the hydrated Li^+ is too large to enter the cavity of β-CD*, exclusion of K^+ and Rb^+ from the β-CD* cavity appears to be a result of the relatively large free energy of hydration of these cations. In the case of the larger γ-CD*, size exclusion seems not possible and the cation hydrophilicity appears to be the sole reason for exclusion of Li^+, K^+, and Rb^+. Therefore, it is not surprising that capacitance measurements indicate some inclusion of Cs^+, which is small and has the lowest free energy of hydration among the investigated alkaline metal cations. A significant but relatively small increase in capacitance was also observed for the tetrabutylammonium cation. The poor hydration of this cation certainly favors inclusion, but the large size of this ion probably imposes a steric hindrance to complete inclusion into the cyclodextrin cavities.

Measurement of Anion Inclusion Constants. The predominantly electrostatic origin for anion inclusion into CD* monolayers is further confirmed by the potential dependence of the NO_3^- inclusion. To show this, we take advantage of the phosphate exclusion and monitor changes in the interfacial capacitance as a function of the nitrate concentration in a 0.10 M phosphate buffer of pH 6.4. Results are shown in Figure 6 for β-CD*-modified Hg electrodes and three values of the electrode potential. As expected, the extent of nitrate inclusion increases as the potential becomes more positive. The lines in the figure represent nonlinear least-squares fits of a Langmuir isotherm to the data. Fitting was performed by expressing the interfacial capacitance as a function of the nitrate concentration in solution. For this purpose, the fractional

(23) Marcus, Y. *Biophys. Chem.* **1994**, *51*, 111.
(24) Hersey, A.; Robinson, B. H.; Kelly, H. C. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 1271.
(25) Cramer, F.; Saenger, W.; Spatz, H.-C. *J. Am. Chem. Soc.* **1967**, *89*, 14.
(26) Yamashoji, Y.; Fujiwara, M.; Matsushita, T.; Tanaka, M. *Chem. Lett.* **1993**, 1029. Gelb, R. I.; Schwartz, L. M.; Radeos, M.; Laufer, D. A. *J. Phys. Chem.* **1983**, *87*, 3349. Rohrbach, R. P.; Rodriguez, L. J.; Eyring, E. M.; Wojcik, F. J. *J. Phys. Chem.* **1977**, *81*, 944.
(27) Buvari, A.; Barcza, L. *Inorg. Chim. Acta* **1979**, *33*, L178. Mochida, K.; Kagita, A.; Matsui, Y.; Date, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3703.
(28) Matsui, Y.; Ono, M.; Tokunaga, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 535.
(29) Godinez, L. A.; Schulze-Fiehn, B.; Patel, S.; Criss, C. M.; Evanseck, J. D.; Kaifer, A. E. *Supramol. Chem.* **1996**, *8*, 17.
(30) Fuhrhop, J.-H.; Krull, M.; Schulz, A.; Möbius, D. *Langmuir* **1990**, *6*, 497.
(31) Ryghkov, G. Y.; Pusch, M.; Roberts, M. L.; Jentsch, T. J.; Bretag, A. H. *J. Gen. Physiol.* **1998**, *111*, 653. Hallani, M.; Lynch, J. W.; Barry, P. H. *J. Membr. Biol.* **1998**, *161*, 163.
(32) Mansoura, M. K.; Smith, S. S.; Choi, A. D.; Richards, N. W.; Strong, T. V.; Drumm, M. L.; Collins, F. S.; Dawson, D. C. *Biophys. J.* **1998**, *74*, 1320. Bormann, J.; Hamill, O. P.; Sakmann, B. *J. Physiol.* **1987**, *385*, 243. Franciolini, F.; Petris, A. *Biochim. Biophys. Acta* **1990**, *1031*, 247. Müller, M.; Schlue, W.-R. *Brain Res.* **1998**, *781*, 307.

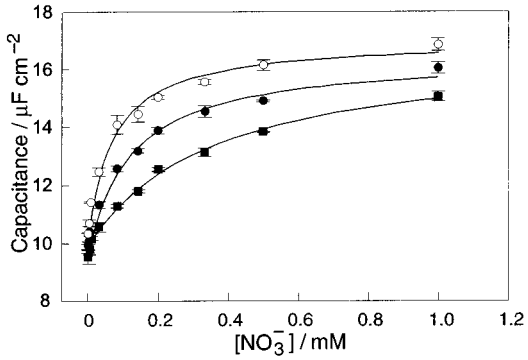

Figure 6. Dependence of the interfacial capacitance of β-CD*-modified Hg electrodes on the concentration of KNO_3 in 0.1 M pH = 6.4 phosphate buffer recorded at −0.25 V (●), −0.30 V (○), and −0.40 V (■). The continuous lines are least-squares fits of eq 4 to the data.

occupancy θ of the CD* sites by nitrate ions is used:

$$\theta = \frac{[(\mathrm{CD^*\cdot NO_3^-})_{ads}]}{[(\mathrm{CD^*\cdot NO_3^-})_{ads}] + [\mathrm{CD^*_{ads}}]} \quad (1)$$

where $[\mathrm{CD^*_{ads}}]$ and $[(\mathrm{CD^*\cdot NO_3^-})_{ads}]$ are the surface concentrations of the free and the occupied cyclodextrin sites, respectively. The relation between the surface concentrations of the free and occupied cyclodextrin sites and the nitrate concentration in solution $[NO_3^-]$ is given by the nitrate inclusion constant $K^{app}_{nitrate}$:

$$K^{app}_{nitrate} = \frac{[(\mathrm{CD^*\cdot NO_3^-})_{ads}]}{[\mathrm{CD^*_{ads}}][\mathrm{NO_3^-}]} \quad (2)$$

Importantly, θ can also be expressed as a function of the interfacial capacitance C:

$$\theta = \frac{C - C_{min}}{C_{max} - C_{min}} \quad (3)$$

where C_{max} represents the capacitance value at a high limit of nitrate concentration and C_{min} is the capacitance in the absence of nitrate ions. Solving the set of eqs 1−3 for C, one obtains a Langmuir isotherm that gives the capacitance as a function of $[NO_3^-]$:

$$C = \frac{C_{max}K^{app}_{nitrate}[\mathrm{NO_3^-}] + C_{min}}{1 + K^{app}_{nitrate}[\mathrm{NO_3^-}]} \quad (4)$$

Langmuir isotherms are fitted by using $K^{app}_{nitrate}$ and C_{max} as fitting parameters. For the example in Figure 6, the $K^{app}_{nitrate}$ values 3.2 ± 0.6, 7.8 ± 2.5, and 16.8 ± 5.6 M^{-1} (confidence intervals for the 95% level) were obtained as fitting parameters at −0.40, −0.30, and −0.25 V versus SCE, respectively. (Incipient calomel formation hinders experiments at much higher potentials.) The electrostatic contribution to the driving force for inclusion of NO_3^- into β-CD* monolayers is clearly confirmed by the increase of the inclusion constant $K^{app}_{nitrate}$ with the electrode potential.

Correcting Apparent Anion Inclusion Constants for the Double-Layer Effect. Using such $K^{app}_{nitrate}$ values, the nitrate occupancy of the CD* monolayers can be calculated as a function of the nitrate concentration in the aqueous solution. Furthermore, the $K^{app}_{nitrate}$ values are needed in the quantitative discussion of binding of neutral compounds to CD* monolayers, as will be shown below. However, $K^{app}_{nitrate}$ values do not only reflect the driving forces for nitrate inclusion into CD* monolayers. Because of the potential drop within the diffuse ionic double layer at the monolayer−solution interface, the concentration of free nitrate at that interface differs from the nitrate concentration in the bulk of the solution. An analogous effect was first discussed for electroactive ions at bare electrodes in Frumkin's classical work on electrode kinetics.[33] In the present case, the concentration of free nitrate at the monolayer−solution interface in the range of potentials positive of E_{pzc} is larger than that in the bulk of the solution. This effect is not related to the anion inclusion event itself and is strongly affected by the ionic strength of the solution. We show in the following how the apparent nitrate inclusion constants $K^{app}_{nitrate}$ can be corrected to give $K^{corr}_{nitrate}$.

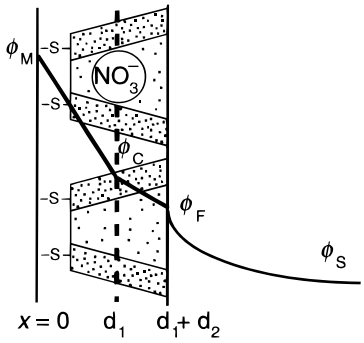

Figure 7. Model for the computation of the interfacial potential drop at the electrode modified with a cyclodextrin monolayer of total thickness $d_1 + d_2$. The metal surface is at $x = 0$. Included nitrate ions are located at $x = d_1$.

In analogy to the case of the Frumkin theory, the concentration of free nitrate at the monolayer−solution interface $[(NO_3^-)_F]$ can be obtained from the potential ϕ_F at the monolayer−solution interface (Figure 7):

$$[(\mathrm{NO_3^-})_F] = [\mathrm{NO_3^-}]e^{-\phi_F F/RT} \quad (5)$$

where F, R, and T have their usual meanings. To determine ϕ_F, we use here a modification of the model developed by Smith and White for the interfacial potential distribution across electroactive monolayers.[34] A scheme showing our model system is shown in Figure 7. It consists of the electrode surface at $x = 0$ and the cyclodextrin monolayer of thickness $d_1 + d_2$. While free nitrate ions can only approach the electrode as close as $d_1 + d_2$, nitrate ions that are included into the cyclodextrin monolayer approach the electrode surface to a distance d_1. The potentials at the electrode surface, at the inclusion sites, at the monolayer−solution interface, and in the bulk are called ϕ_M, ϕ_C, ϕ_F, and ϕ_S, respectively, and can be determined by using Gauss's law and the Gouy−Chapman model.

The charge density in the plane of nitrate inclusion is a function of the total surface concentration Γ of the cyclodextrins and their nitrate occupancy θ:

$$\sigma_C = -F\theta\Gamma \quad (6)$$

The nitrate occupancy of the cyclodextrin monolayer can be formulated, analogously as in a similar treatment for acidic monolayers,[11] as follows:

(33) Frumkin, N. A. *Z. Phys. Chem. (Leipzig)* **1933**, *164A*, 121.
(34) Smith, C. P.; White, H. S. *Anal. Chem.* **1992**, *64*, 2398.

$$\log\{(1-\theta)/\theta\} = -\log\{[NO_3^-]\} + \log\{K_{nitrate}\} + \{F(\phi_F - \phi_S)/2.3RT\} \quad (7)$$

Setting ϕ_S to zero allows us to replace ϕ_M with $E_{appl} - E_{pzc}$, where E_{appl} is the applied potential. Numerically solving the set of eqs 6 and 7 from this article as well as eqs 10a−10d from Smith and White[34] (replacing there ϕ_{PET} with ϕ_C, σ_{PET} with σ_C, as well as ϵ_1 and ϵ_2 with ϵ_{ml}) after elimination of θ, ϕ_C, σ_M, σ_C, and σ_{dif} and insertion of appropriate values for the parameters Γ, d_1, d_2, ϵ_3, ϵ_{ml}, κ, and E_{pzc} allows the determination of ϕ_F. For the present case, we used the Γ values determined voltammetrically. The monolayer thickness $d_1 + d_2$ was estimated from CPK models to be 0.85 nm. The dielectric constants of the electrolyte solution ϵ_3 and the monolayer ϵ_{ml} were set to 78 and 10, respectively. The latter value was deduced from d_2 and the experimental capacitances C of the CD*-modified electrodes in phosphate buffer solution, using the relation $C = \epsilon\epsilon_{ml}/(d_1 + d_2)$. As described above, E_{pzc} was approximated with −0.65 V. Only for d_1 could an estimate supported by experimental evidence not be obtained. However, computation of ϕ_F for d_1 values between $0.2(d_1 + d_2)$ and $0.8(d_1 + d_2)$, a constant total membrane thickness $d_1 + d_2$, and an otherwise constant set of parameters showed that d_1 had a very small effect on ϕ_F of only a few millivolts. Because of this relative insensitivity to d_1 and also in view of the results discussed in the following section, d_1 was set to $0.66(d_1 + d_2)$. Good estimates of ϕ_F can be obtained by use of the experimental $K^{app}_{nitrate}$ as an approximation for $K_{nitrate}$. Further minor improvements are obtained from iterative reevaluation of ϕ_F by use of $K^{corr}_{nitrate}$ for $K_{nitrate}$.

For an applied voltage of −0.3 V, values of ϕ_F computed according to the procedure described above were found to be on the order of 30 mV for nitrate-free 0.1 M phosphate buffer solutions. On the other hand, ϕ_F was found to be close to 0 mV at high nitrate concentrations. This large dependence of ϕ_F on the solution composition shows that free nitrate concentrations at the monolayer−solution interface cannot be obtained from the solution concentration by correction with a constant factor. Therefore, to obtain nitrate inclusion constants that are more representative for the inclusion forces at the monolayer than the apparent constants $K^{app}_{nitrate}$, values of ϕ_F computed for each monolayer type and each nitrate concentration were used in conjunction with eq 5 to calculate the corresponding concentrations of free nitrate $[(NO_3^-)_F]$ at the monolayer−solution interfaces. Fits of eq 4 to the data consisting of these corrected nitrate concentrations and the experimental capacitances provided the desired $K^{corr}_{nitrate}$. For example, the previously mentioned values of 3.2, 7.8, and 16.8 M^{-1} for $K^{app}_{nitrate}$ at −0.40, −0.30, and −0.25 V versus SCE for β-CD* correspond to 2.0 ± 0.5, 5.2 ± 2.0, and 12.9 ± 2.6 M^{-1} (confidence intervals for the 95% level) for $K^{corr}_{nitrate}$, respectively. This shows that these Frumkin type corrections reveal somewhat smaller binding constants than would be expected from uncorrected data sets. This is indeed what is expected qualitatively for potentials positive of E_{pzc}.

One might ask why these experiments have not been performed with a higher background of excluded electrolyte ions, possibly eliminating the need for the correction of the nitrate concentrations. However, computations show that for low nitrate concentrations ϕ_F takes values of more than 10 mV even when the phosphate buffer concentration is as high as 1 M. A second point that is worth mentioning also concerns ϕ_F. The computation of ϕ_F with a simpler model of a completely anion-excluding monolayer of $\epsilon_{ml} = 10$ and a thickness of 0.85 nm suggests much more significant corrections of the nitrate inclusion constants. For example, the $K^{app}_{nitrate}$ of 16.8 M^{-1} at −0.25 V versus SCE for β-CD* would be corrected to 7.3 M^{-1}. The overcorrections of $K^{app}_{nitrate}$ suggested by this simple model are the consequence of ϕ_F values of more than 10 mV even at high nitrate concentrations. Such unrealistically large values for ϕ_F are obtained because this simple model cannot take into account that nitrate anions enter the cyclodextrins at these high nitrate concentrations. However, in view of the evidence for anion inclusion presented in this paper, such a simple model seems not justifiable.

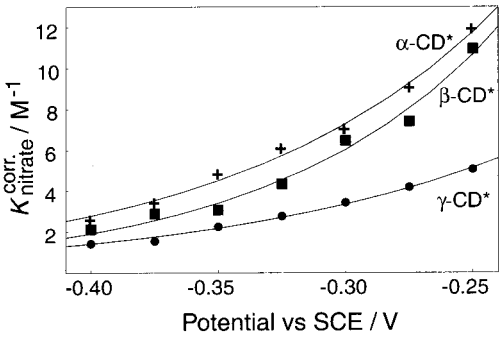

Figure 8. Potential dependence of the nitrate inclusion constant $K_{nitrate}$ for α-CD*-, β-CD*-, and γ-CD*-modified Hg electrodes in 0.50 M KNO_3, 0.1 M phosphate buffer (pH = 6.4). The continuous line is a least-squares fit of eq 8 to the experimental data.

Potential Dependence of Nitrate Inclusion. To discuss the electrostatic contribution of the applied potential on the inclusion event more quantitatively, $K^{corr}_{nitrate}$ can be expressed as a function of the applied potential:

$$\ln(K^{corr}_{nitrate}) = \ln(K^{pzc}_{nitrate}) - (zF/RT)r(E - E_{pzc}) \quad (8)$$

where E is the applied potential, $K^{pzc}_{nitrate}$ is the constant for nitrate inclusion into the interfacial cyclodextrin monolayer at the potential of zero charge E_{pzc}, and r stands for the fraction of the interfacial potential drop that is acting on the included nitrate ions. Fitting experimental data with eq 8 allows us to determine $K^{pzc}_{nitrate}$ and r as fitting parameters. For β-CD* monolayers, the resulting values are 0.11 ± 0.08 M^{-1} and 0.29 ± 0.05 (confidence intervals for the 95% level), respectively. As shown in Figure 8, this plain model describes the potential dependence of $K^{corr}_{nitrate}$ rather well. The extremely small value of $K^{pzc}_{nitrate}$ shows that the nonelectrostatic contribution to nitrate inclusion is negligible. Similar results can be obtained for nitrate inclusion into α-CD* (0.25 ± 0.11 M^{-1}) and γ-CD* (0.17 ± 0.05 M^{-1}) monolayers. On the other hand, a somewhat larger value of 1.7 M^{-1} is obtained for perchlorate inclusion into β-CD* monolayers, which agrees with the more lipophilic nature of this anion.[21]

A second interesting result is the value of r. If it is assumed that the potential across the cyclodextrin monolayer falls linearly with the distance from the electrode surface, as it appears at least reasonable at low nitrate concentrations, it can be inferred from the value of $r = 0.29 \pm 0.05$ for β-CD* monolayers that the bound nitrate ions are on average separated from the electrode surface by two-thirds of the total monolayer thickness. Since the large CH_2S substituents of the cyclodextrins face the electrode, the nitrate ions seem to be located on average

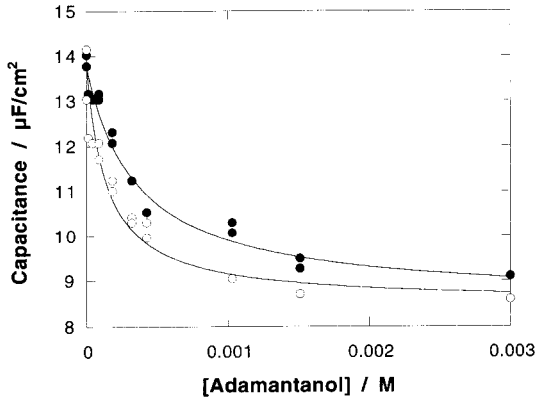

Figure 9. Dependence of the interfacial capacitance of the (●) β-CD*- and (○) γ-CD*-modified Hg electrodes on the concentration of 1-adamantanol recorded in 0.50 M KNO_3, 0.1 M pH = 6.4 phosphate buffer at −0.30 V versus SCE. The continuous lines are least-squares fits of eq 6 to the data.

close to the center of the cyclodextrin cavities. Similar results can be obtained for nitrate inclusion to α-CD* ($r = 0.25 \pm 0.03$) and γ-CD* ($r = 0.22 \pm 0.02$) monolayers as well as for perchlorate inclusion into β-CD* monolayers ($r = 0.33$).

Binding of Uncharged Guests to Cyclodextrin Monolayers. The interfacial capacitances of a CD*-coated electrode when measured with an excluded anion electrolyte such as phosphate are within error identical to those measured with a phosphate buffer solution containing adamantanol. Therefore, such capacitance measurements cannot be used to follow adamantanol−CD* binding directly. However, competitive binding of uncharged species with anions such as nitrate allows us to monitor the host−guest interactions of the uncharged species with CD* monolayers. As an example, consider the data in Figure 9 reflecting capacitance changes as a function of 1-adamantanol (A), an alcohol known to partition into β- and γ-cyclodextrins. Since 1-adamantanol binding in the CD* cavities requires exclusion of the nitrate ions, the capacitance decreases with increasing 1-adamantanol concentration [A]. The fractional occupancy θ of the cyclodextrin sites with nitrate can be defined in analogy to eq 1:

$$\theta = \frac{[(CD^*\cdot NO_3^-)_{ads}]}{[(CD^*\cdot NO_3^-)_{ads}] + [(CD^*\cdot A)_{ads}] + [CD^*_{ads}]} \quad (9)$$

where $[(CD^*\cdot A)_{ads}]$ is the surface concentration of the 1-adamantanol complexes. The latter is related to the 1-adamantanol concentration in solution through the adamantanol binding constant K_A:

$$K_A = \frac{[(CD^*\cdot A)_{ads}]}{[CD^*_{ads}][A]} \quad (10)$$

Moreover, because C_{min} does not depend on the 1-adamantanol concentration, θ is again given by eq 3. Solving the set of eqs 2, 3, 9, and 10 for C gives

$$C = \frac{C_{min} + C_{min}K_A[A] + C_{max}K_{nitrate}[NO_3^-]}{1 + K_{nitrate}[NO_3^-] + K_A[A]} \quad (11)$$

A fit of the data shown in Figure 8 with eq 11 and K_A and C_{max} as fitting parameters allows the determination of the binding constant for 1-adamantanol K_A. The thus obtained K_A values for −0.3 V are $10^{4.04}$ M^{-1} ($CI_{95\%}$ $10^{3.62}$ to $10^{4.25}$ M^{-1}) and $10^{4.46}$ M^{-1} ($CI_{95\%}$ $10^{3.96}$ to $10^{4.67}$ M^{-1}) for the β-CD* and γ-CD* monolayers, respectively. While no binding of 1-adamantanol to α-CD* could be observed, the smaller guest 1-hexanol was found to bind to this smaller cyclodextrin with a $K_{1-hexanol}$ of $10^{5.00}$ M^{-1} at −0.3 V.

The series of K_A values for binding of 1-adamantanecarboxylate to nonderivatized α-cyclodextrin (1.4×10^2 M^{-1}), β-cyclodextrin (2.0×10^4 M^{-1}), and γ-cyclodextrin (3.0×10^3 M^{-1})[35] in homogeneous aqueous solution (0.01 M phosphate buffer, 25 °C) reflects similarly that the small cavities of α-cyclodextrins are too small for inclusion of the adamantyl group, which is roughly spherical and has a diameter of about 6.5 Å. On the other hand, in homogeneous solution the smaller guest 1-hexanol binds well to nonderivatized α-cyclodextrin (8.9×10^2 M^{-1}).[36] Unfortunately, data on binding of adamantanol derivatives and alkanols to permethylated cyclodextrins are few. However, a number of studies of complexes of permethylated β-cyclodextrins with several types of guests have shown that permethylation of the secondary hydroxyl groups significantly affects the properties of cyclodextrins by elimination of the conformation-stabilizing intramolecular hydrogen bonds, by changing the diameter at the upper rim of the cyclodextrin cavity, by enhancing the flexibility of the host, and by increasing the hydrophobicity of its upper rim.[37,38] It has been shown for β-cyclodextrin that permethylation weakens binding of 1-admantanylammonium, 1-adamantanecarboxylate, and adamantane-1-acetate, which all seem to ideally fit the cavity of nonderivatized β-cyclodextrin.[39] Similar effects may explain the weaker binding of 1-adamantanol to β-CD* monolayers than to γ-CD* monolayers, which contrasts with the stronger binding of 1-adamantanecarboxylate to nonderivatized β- than to nonderivatized γ-cyclodextrin in homogeneous solution. It appears to be the result of a destabilizing effect of permethylation for the adamantanol complex of β-CD* and an analogous stabilizing effect of the adamantanol complex of γ-CD*, whose cavity in the nonmethylated state is somewhat too large for this guest. On the other hand, the relatively large value of $K_{1-hexanol}$ for α-CD* monolayers is probably the result of the permethylation of the secondary hydroxyl groups. A trend for stronger binding to α-cyclodextrins upon permethylation has been observed repeatedly[38,40] and can be explained by the enlargement of the hydrophobic cavity. A more quantitative discussion of the K_A values based on comparison with complexation equilibria in homogeneous solution is a priori problematic because binding in solution and at interfaces can differ substantially in strength and selectivity.[41,42] Moreover, because literature data on complexation at cyclodextrin monolayers are scarce, it is not possible to compare these K_A values to values determined elsewhere for monolayers.

(35) Cromwell, W. C.; Byström, K.; Eftink, M. R. *J. Phys. Chem.* **1985**, *89*, 326.
(36) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808.
(37) Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 497. Bertrand, G. L.; Faulkner, J. R., Jr.; Han, S. M.; Armstrong, D. W. *J. Phys. Chem.* **1989**, *93*, 6863. Kano, K.; Ishimura, T.; Negi, S. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, *22*, 285.
(38) Botsi, A.; Yannakopoulou, K.; Perly, B.; Hadjoudis, E. *J. Org. Chem.* **1995**, *60*, 4017. Hendrickson, K.; Easton, C. J.; Lincoln, S. F. *Aust. J. Chem.* **1995**, *48*, 1125.
(39) Gelb, R. I.; Raso, S.; Alper, J. S. *Supramol. Chem.* **1995**, *4*, 279−285. Gelb, R. I.; Schwartz, L. M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, *7*, 537.
(40) Casu, B.; Reggiani, M.; Sanderson, G. R. *Carbohydr. Res.* **1979**, *76*, 59.
(41) Ariga, K.; Kunitake, T. *Acc. Chem. Res.* **1998**, *31*, 371.
(42) Xiao, K. P.; Bühlmann, P.; Umezawa, Y. *Anal. Chem.* **1999**, *71*, 1183.

Cyclodextrin Monolayers on Gold. Because Au may be more suited for routine analysis applications than Hg, we explored the possibility of anion inclusion in cyclodextrin monolayers on Au electrodes modified with β-CD*. Dipping an electrode in 0.5 M KOH and scanning the potential from -0.6 to -1.2 V versus SCE showed a peak for reductive desorption of β-CD* at -1.04 V. Integration of the reduction current gave a charge of 49 μC/cm^2. Taking into account a surface roughness factor of approximately 1.2 and assuming that seven gold−thiolate bonds are reductively broken for each β-CD* molecule, this charge corresponds to a mean molecular area of 251 Å^2/molecule and a surface coverage of 6.1×10^{-11} mol/cm^2. The latter value is somewhat larger than the value 4.8×10^{-11} mol/cm^2 reported by Kaifer and co-workers[3] for SAMs of a nonmethylated isomeride of β-CD*. This difference notwithstanding, the coverage of β-CD* on Au was significantly lower than that for SAMs of β-CD* on mercury electrodes. In agreement with earlier results for cyclodextrin SAMs on Au,[4,5,14,15,43] it can be concluded also that β-CD* SAMs on gold are not very well packed. It appears likely that the limited lateral mobility of the cyclodextrin oligothiols on gold explains this finding.

Nevertheless, nitrate inclusion into β-CD* monolayers on gold electrodes was evidenced by interfacial capacitance measurements. Because of the high E_{pzc} of gold,[44] these measurements were performed in a range of much higher potentials than that in the case of Hg. The capacitances in the range from $+0.35$ to $+0.1$ V versus SCE were consistently larger when measured with phosphate buffer containing 0.05 M nitrate than when measured with phosphate buffer only or with phosphate buffer containing 0.05 M NaF. At $+0.3$ V, for example, the ratio of the capacitances for nitrate-containing and nitrate-free solutions was 1.26 ± 0.15. On the other hand, control experiments with fluoride solutions gave a ratio of 0.99 ± 0.13. The somewhat smaller effect of nitrate than in the case of the β-CD*-modified mercury electrodes is certainly partly related to the smaller β-CD* coverage. Unfortunately, efforts to backfill intermolecular voids in β-CD* SAMs on gold by brief exposure of β-CD* SAMs to solutions of 1-adamantanol and 1-octanethiol[3] did not, so far, increase but unexpectedly minimized the effect of nitrate on the capacitance. It appears that our experimental conditions are not yet optimized enough to exclude octanethiol from the cyclodextrin cavities, as it was intended by backfilling in the presence of 1-adamantanol.

(43) Beulen, M. W. J.; Bügler, J.; Lammerink, B.; Geurts, F. A. J.; Biemond, E. M. E. F.; van Leerdam, K. G. C.; van Veggel, F. C. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Langmuir* **1998**, *14*, 6424.

(44) Kolb, D. M. In *Structure of Electrified Surfaces;* Lipkowski, J., Ross, P. N., Eds.; VCH Publishers: Weinheim, 1993; p 65.

Conclusions

We showed that double-layer electrostatic forces induce inclusion of inorganic cations and anions into monolayer films of α-, β- and γ-thiocyclodextrins. This process is accompanied by an increase in the interfacial capacitance and exhibits ion selectivity. Anion inclusion constants can be determined by analyzing the dependence of the interfacial capacitance on the concentration of the anions with a Langmuir isotherm. Their potential dependence allows us to distinguish between the electrostatic and nonelectrostatic contributions to the total driving force for anion inclusion. Furthermore, competitive binding of hydrophobic molecules such as 1-adamantanol or 1-hexanol decreases interfacial capacitances. This shows that changes of the capacitance of the CD*-modified interface can serve as a general signal transduction mode and can be used to monitor host−guest interactions at monolayers. Extension of these types of measurements into solid electrodes and application of other selective monolayer type coatings open a possibility of designing a novel class of electrochemical sensors analogous to that of the ion-channel-mimetic sensors.[45] In contrast to the latter, addition of an electroactive species to the sample solutions is not required in the case of the detection mode presented here.

Acknowledgment. We thank Nobuaki Kimura for his help in the synthesis of per-(6-deoxy-6-bromo)-γ-cyclodextrin and Michael Wittek for his assistance with Figure 3. The kind synthetic advice of Dr. Waichiro Tagaki is gratefully acknowledged. This research was supported by a cooperative science program of the Japanese Society for the Promotion of Science and the U.S. National Science Foundation. In Berkeley, the project was supported by the National Science Foundation through Grants CHE-9422619 and INT-9513140 and by the Microsensor Research Division of Sandia National Laboratory. In Tokyo, it was supported by Grants for Scientific Research from the Ministry of Education, Science and Culture including a Grant-in-Aid for Scientific Research for the priority area of "Electrochemistry of Ordered Interfaces" No. 10131216.

Supporting Information Available: A detailed description of the synthesis and spectroscopic product characterization of α-, β-, and γ-CD* (2 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

LA990826I

(45) Bühlmann, P.; Aoki, H.; Xiao, K. P.; Amemiya, S.; Tohda, K.; Umezawa, Y. *Electroanalysis* **1998**, *10*, 1149.