Effect of Cyclodextrin Charge on Complexation of Neutral and Charged Substrates: Comparison of $(SBE)_{7M}$-β-CD to HP-β-CD

V. Zia, [1,3] R. A. Rajewski,[2] and V. J. Stella[1,2,4]

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Purpose. To understand the role of charge in substrate/cyclodextrin complexation by comparing the binding of neutral and charged substrates to a neutral cyclodextrin, such as hydroxypropyl β-CD (HP-β-CD) with 3.5 degrees of substitution, and an anionically charged cyclodextrin, such as sulfobutyl ether β-CD ($(SBE)_{7M}$-β-CD) with 6.8 degrees of substitution.

Method. HP-β-CD and $(SBE)_{7M}$-β-CD were evaluated in their ability to form inclusion complexes with neutral compounds, as well as to cationic and anionic substrates in their charged and uncharged forms. The complexation constants (K_c) were determined via a UV spectrophotometric technique, by monitoring the change in substrate absorbance upon incremental addition of a concentrated cyclodextrin solution. The role of electrostatic interaction was probed by observing K_c as a function of solution ionic strength.

Results. Neutral molecules displayed a stronger interaction with $(SBE)_{7M}$-β-CD compared to HP-β-CD. In those cases where the guest possessed a charge (positive or negative), HP-β-CD/substrate complexes exhibited a decrease in complexation strength (2 to 31 times lower) compared to the neutral forms of the same substrate. The same was true (but to a larger extent, 41 times lower) for negatively charged molecules binding to $(SBE)_{7M}$-β-CD due to charge-charge repulsion. However, positively charged molecules interacting with the negatively charged $(SBE)_{7M}$-β-CD displayed a similar binding capability as their neutral counterpart, due to charge-charge attraction. Further evaluation through manipulation of solution ionic strength revealed strong electrostatic interactions between substrate and cyclodextrin charges. In addition, the studies suggested that on average two sulfonates out of seven may be involved in forming ionic attraction or repulsion effects with the positive charges on prazosin and papaverine, or negative charges of ionized naproxen and warfarin.

Conclusions. Presence of charge on the cyclodextrin structure provides an additional site of interaction compared to neutral cyclodextrins, which may be modified using solution ionic strength.

KEY WORDS: cyclodextrins; ionic strength; coulombic interactions; sulfobutyl cyclodextrins; hydroypropyl cyclodextrin.

INTRODUCTION

Although numerous natural and modified cyclodextrins have been described in the literature, there are only six types of cyclodextrins to date that are produced on an industrial scale for pharmaceutical use. These consist of the three parent cyclodextrins (α-, β-, and γ-CDs) and three classes of modified cyclodextrins, namely, methylated, hydroxypropylated and sulfobutylated cyclodextrins (1). Naturally produced cyclodextrins, excluding γ-CDs, along with methylated cyclodextrins have no significant use in parenteral dosage forms due to toxicity issues (2). However, HP-β-CD and $(SBE)_{7M}$-β-CD have recently gained considerable attention in the class of modified β-CDs because of their improved safety profiles (1,2).

HP-β-CD and $(SBE)_{7M}$-β-CD are highly soluble compounds capable of forming reversible inclusion complexes with a variety of molecules to form soluble complexes. HP-β-CD is derived by substitution of either primary or secondary hydrogen of the hydroxyl group of β-CD with a 2-hydroxypropyl moiety (3). As shown in Figure 1, there are 21 possible sites where hydroxypropyl groups can attach to the cyclodextrin torus. In the case of the specific HP-β-CD used in this study, an average of approximately 3.5 hydroxypropyl groups are attached to the torus. The $(SBE)_{7M}$-β-CD is derivatized in a similar manner, with the exception that the substituents are sulfobutyl groups (4). $(SBE)_{7M}$-β-CD has an average of 6.8 substituents per cyclodextrin, and therefore has about seven negative charges associated with it, which are counterbalanced with sodium ions (Fig. 1).

Because of the different substituents placed on the cyclodextrins, HP-β-CD and $(SBE)_{7M}$-β-CD have properties that differ from one another. The charged sulfonate groups of sulfobutyl ether moieties provide a charged head group in addition a hydrophobic tail group that are attached to the cyclodextrin cavity. Usually, placing a charged group on or around the cyclodextrin cavity reduces its complexation ability (4–7). Neutral guests interacting with charged cyclodextrins generally show lower stability constants relative to similar neutral cyclodextrins. This decrease in apparent binding has been associated with changes in the hydrophobicity of the cavity interior and/or changes in geometry of inclusion complexation (5,7). Unlike most other charged cyclodextrins, $(SBE)_{7M}$-β-CD often shows superior binding to most neutral substrates, due to the significant separation of the charged sulfonate moiety from the cyclodextrin torus and the interaction of some substrates with portions of the butyl moiety (8,9). In some cases, where oppositely charged molecules and charged cyclodextrins interacted, strong complexations have been observed (7–12). In such cases, the improvement in complexation has been associated with additional interaction sites provided by the cyclodextrin charge. The mode of interaction is presumed to be hydrophobic interaction with the cavity interior along with additional charge-charge interaction between the charged guest and host.

In the present work, the interaction of neutral (HP-β-CD) and charged ($(SBE)_{7M}$-β-CD) cyclodextrins with various neutral, anionic, and cationic molecules were studied. The two cyclodextrins resemble each other in providing not only a hydrophobic cavity, but also the potential for additional surfaces of interaction. However, $(SBE)_{7M}$-β-CD may provide supplementary binding sites for molecules capable of forming ionic interactions with the charged sulfonate moieties. Thus, the role of charge interactions between the guest and the host, was the primary focus of this study.

[1] Department of Pharmaceutical Chemistry, The University of Kansas, 2095 Constant Avenue, Lawrence, Kansas 66047.
[2] Higuchi Biosciences Center for Drug Delivery Research, The University of Kansas, 2095 Constant Avenue, Lawrence, Kansas 66047.
[3] Present address: Department of Formulation, Pharmacia, 4901 Searle Pkwy, Skokie, Illinois 60077.
[4] To whom correspondence should be addressed. (e-mail: stella@ku.edu)

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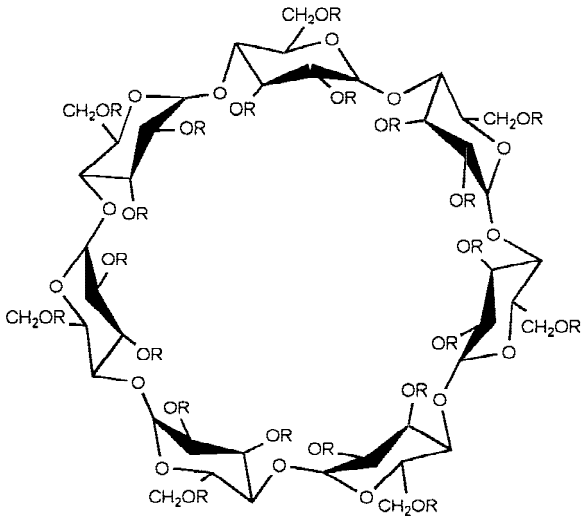

$(SBE)_{7M}$-β-CD; R = $[-(CH_2)_4SO_3^-Na^+]_{6.8}$ or H

HP-β-CD; R = $-(CH_2CH(CH_3)OH)_{3.5}$ or H

Fig. 1. Structural representation of HP-β-CD and $(SBE)_{7M}$-β-CD.

EXPERIMENTAL

Materials

All substrates and their sources were identical to those described and defined previously (9). HP-β-CD (Lot 92-3, MW 1338; TDS 3.5; water content = 7.4%) was obtained form Cerestar (Hammond, Indiana), previously known as American-Maize Products. The preparation and characterization of $(SBE)_{7M}$-β-CD (MW 2207.6; TDS 6.8; water content = 9.8%) and its derivatives have also been described previously (9). All cyclodextrins were corrected for water content prior to use. Water was deionized and charcoal filtered prior to glass distillation, using a Corning Mega-Pure™ System MP-1 (Corning, New York).

Instrumentation

Karl Fischer water analyses of cyclodextrins were performed on a Brinkmann 652 KF-Coulometer. UV analysis was performed using a Perkin Elmer Double beam UV/Vis Lambda 6 instrument equipped with a data manager software program and a water-jacketed multicel attachment. A circulating water bath was used to provide constant temperature during experiments.

Method

The cyclodextrin complexation constants were determined by monitoring the change in substrate UV absorbance upon the incremental addition of a concentrated cyclodextrin solution (13). Complexation constants were determined via reciprocal plots. Specifics of the actual procedure were described in an earlier paper (9). The drug concentration and the pH values studied were also mentioned previously. Because some of the agents were studied in both ionized and unionized states, Table I describes those conditions that differed from the earlier study.

Ionic Strength Effects

To better determine the effects of charge interactions, solutions of varying ionic strength (I = 0.01, 0.1, 0.2, 0.3 M) were prepared at the appropriate pH values to form the neutral or charged form of the molecules under investigation. Solution ionic strength was determined by the buffer and the NaCl salt added, while assuming substrate and cyclodextrin contribution to be minimal and negligible since substrate concentrations were generally below 10^{-5} M and cyclodextrin concentration ranges were 10^{-5}–10^{-3} M. The complexation constants of molecules to cyclodextrins were determined at a fixed pH value with varying ionic strength.

RESULT AND DISCUSSION

Complexation of Neutral Molecules to $(SBE)_{7M}$-β-CD and HP-β-CD

The complexation constants of ten unionized molecules with HP-β-CD and $(SBE)_{7M}$-β-CD were determined and the results are reported in Table II along with the K_c ratio of $(SBE)_{7M}$-β-CD over HP-β-CD. All complexes exhibited linear x-reciprocal plots, suggesting a 1:1 substrate/cyclodextrin complexation (9). The negatively charged $(SBE)_{7M}$-β-CD uniformly showed larger complexation capability over HP-β-CD, but the extent of increase in complexation was not the same for all molecules. Molecules such as hydrocortisone, prednisolone, and methylprednisolone showed only a slight increase in complexation (1.2–1.4 times), while molecules such as testosterone, benzylguanine, and prazosin showed more significant improvements of 3.2–9.1 times in their binding constants.

The stronger complexation ability of $(SBE)_{7M}$-β-CD over HP-β-CD may be attributed to several reasons. The charged sulfonate moieties of $(SBE)_{7M}$-β-CD are not expected to fold back into the cyclodextrin cavity, eliminating any intra- or inter-molecular complexation similar to those associated with the HP-β-CD (1,14). In addition, the charged sulfonate groups of each cyclodextrin are likely to repel one another by extending out and away form each other, providing a hydrophobic region near the cavity composed of only the alkyl ether portions of the sulfobutyl groups. Therefore,

Table I. Conditions Different than Those Described Previously (9) in Determining Complexation (K_c) of Charged and Uncharged Species to Cyclodextrins

Substrate	MW	pKa	λ (nm)	pH	Conc. (μg/ml)[d]
Naproxen	230.3	4.8	213	7.0[a], 2.0[b]	2.5
Warfarin	330.3	4.8	282	7.0[a], 2.0[b]	20
Prazosin	419.9	6.5	250	12.0[c], 2.0[b]	7
Papaverine	375.9	8.1	237	12.0[c], 2.0[b]	6

[a] 50 mM Phosphate buffer.
[b] 10 mM HCl solution.
[c] 10 mM sodium hydroxide solution.
[d] Drug solution concentration at which the experiments were performed.

Table II. Comparison of HP-β-CD to $(SBE)_{7M}$-β-CD in Forming Inclusion Complexes with Neutral Forms of Various Substrates[a]

Substrate	Cyclodextrin	K_c [M^{-1}]	Mean error	K_{Ratio}[b]
Hydrocortisone	HP-β-CD	2056	82	1.22
Hydrocortisone	$(SBE)_{7M}$-β-CD	2516	106	
Prednisolone	HP-β-CD	1319	95	1.38
Prednisolone	$(SBE)_{7M}$-β-CD	1821	58	
Methylprednisolone	HP-β-CD	563	18	1.27
Methylprednisolone	$(SBE)_{7M}$-β-CD	726	32	
Benzylguanine	HP-β-CD	307	7	3.24
Benzylguanine	$(SBE)_{7M}$-β-CD	994	48	
Testosterone	HP-β-CD	11685	91	4.34
Testosterone	$(SBE)_{7M}$-β-CD	50728	918	
Progesterone	HP-β-CD	14856	153	1.79
Progesterone	$(SBE)_{7M}$-β-CD	26644	34	
Naproxen	HP-β-CD	5160	40	1.92
Naproxen	$(SBE)_{7M}$-β-CD	9913	336	
Warfarin	HP-β-CD	902	14	2.29
Warfarin	$(SBE)_{7M}$-β-CD	2063	32	
Prazosin	HP-β-CD	2405	80	4.88
Prazosin	$(SBE)_{7M}$-β-CD	11733	138	
Papaverine	HP-β-CD	80	8	9.06
Papaverine	$(SBE)_{7M}$-β-CD	725	68	

[a] Experiments were performed at 25°C and the appropriate pH value for the dominant presence of neutral species. The derived K_c values are the average of two experiments.
[b] Ratio of $(SBE)_{7M}$-β-CD over HP-β-CD.

complexation of neutral molecules to $(SBE)_{7M}$-β-CD may occur not only via the cyclodextrin cavity, but also the alkyl chains near the cavity (9). In addition to these differences, specific interactions between the various substrates and the two cyclodextrins may be important. Perhaps hydrogen bonding interactions with strategically placed hydrogen bond donor or acceptor groups on the substrates or the cyclodextrin could account for some of the differences observed.

Ionic Strength Effects on Complexation of Neutral Molecules

The effect of solution ionic strength on the complexation constants of various neutral molecules to HP-β-CD and $(SBE)_{7M}$-β-CD is presented in Table III. The effect of ionic strength on the complexation ability of each cyclodextrin was varied. Hydrocortisone and prazosin displayed no significant change in complexation to either cyclodextrin upon increasing ionic strength. However, complexation of both cyclodextrins to warfarin increased as the ionic strength was increased. This increased complexation of warfarin was of similar magnitude for both cyclodextrins. Naproxen was the only molecule that showed a difference in complexation ability to the two cyclodextrins with increasing ionic strength. A significant increase in K_c value of naproxen/$(SBE)_{7M}$-β-CD complex was observed with increasing ionic strength. However, naproxen/HP-β-CD complex did not show an effect in complexation strength upon increasing ionic strength.

To a certain extent, the increased binding of some molecules upon increased ionic strength can be explained by salting out effects. According to the hydrophobic bond concept, the aqueous solubility of hydrophobic molecules may be decreased with an increase in salt concentration (15,16). The increase in complexation constants (K_c) of some molecules with HP-β-CD and $(SBE)_{7M}$-β-CD may be attributed to the same effect, where the interaction of the molecule with the hydrophobic cyclodextrin cavity is increased with addition of electrolytes. However, this phenomenon does not seem to affect all complexes or affect them to the same extent, possibly due to various substrate/CD complexation positions, strengths, geometry, and specific interactions.

Complexation of Charged Species to $(SBE)_{7M}$-β-CD and HP-β-CD

Table IV shows the K_c values for various anionic and cationic molecules in their charged and uncharged states with HP-β-CD and $(SBE)_{7M}$-β-CD, with the K_c ratio of neutral over charged substrates in the last column. The complexation of all molecules with HP-β-CD was decreased upon substrate ionization (positive or negative), but the extent of the decrease was not uniform for each complex. As shown in the last column of Table IV, for HP-β-CD complexes, warfarin displayed the smallest change, while prazosin showed the largest change. For $(SBE)_{7M}$-β-CD complexes, change was dependent on the charge of the guest molecule. Positively charged molecules maintained their complexation strength compared to their neutral forms. However, negatively charged molecules showed decreased complexation. This reduction in complexation strength for anionic molecules to $(SBE)_{7M}$-β-CD was larger than those seen with HP-β-CD.

It has been shown that the complexation strength of molecules to cyclodextrins decreases with an increase in the hydrophilicity of the substrate (17–19). This is attributed to the much simplified rule of "like-dissolves-like." With an increase in the hydrophilicity of the substrate, such as the addition of a charged or hydrophilic moiety, an improved interaction with the polar solvent occurs, lowering the cyclodextrin complexation strength. This has been further established by changing the polarity of the solvent (20–22). The interaction of a molecule in an aqueous solution of cyclodextrin may be

Table III. Effect of Ionic Strength on Complexation (K_c) of Neutral Molecules to HP-β-CD (HP) and $(SBE)_{7M}$-β-CD (SBE), Using NaCl to Control the Ionic Strength (I) at 0.01, 0.1, 0.2, and 0.3 M[a]

	Hydrocortisone		Naproxen		Warfarin		Prazosin	
I	HP	SBE	HP	SBE	HP	SBE	HP	SBE
0.01	1730 ± 28	2090 ± 38	4868 ± 77	7441 ± 83	816 ± 17	1670 ± 93	1729 ± 104	9944 ± 291
0.1	1760 ± 22	2360 ± 46	4962 ± 162	8887 ± 18	765 ± 14	1771 ± 91	2128 ± 227	10591 ± 87
0.2	1810 ± 14	2480 ± 93	5236 ± 330	10747 ± 112	80 ± 12	2022 ± 88	2414 ± 109	9425 ± 39
0.3	1800 ± 61	2600 ± 39	5573 ± 88	11693 ± 620	955 ± 68	2307 ± 145	2028 ± 142	11532 ± 550

[a] The K_c results are expressed in M^{-1} as the mean of two experiments along with their deviation.

Table IV. Complexation of Anionic and Cationic Molecules in Their Charged and Neutral Forms to HP-β-CD and $(SBE)_{7M}$-β-CD at 25°C, and $I = 0.15$ M[a]

Substrate	Cyclodextrin	K_c [M^{-1}]	Mean error	$K_{neutral/charged}$
Naproxen	HP-β-CD	5160	40	7.75
Naproxen(−)	HP-β-CD	665	39	
Naproxen	$(SBE)_{7M}$-β-CD	9913	336	41.7
Naproxen(−)	$(SBE)_{7M}$-β-CD	238	15	
Warfarin	HP-β-CD	902	14	2.08
Warfarin(−)	HP-β-CD	433	25	
Warfarin	$(SBE)_{7M}$-β-CD	2063	32	15.9
Warfarin(−)	$(SBE)_{7M}$-β-CD	130	7	
Prazosin	HP-β-CD	2405	80	31.3
Prazosin(+)	HP-β-CD	78	8	
Prazosin	$(SBE)_{7M}$-β-CD	11733	138	1.05
Prazosin(+)	$(SBE)_{7M}$-β-CD	11202	529	
Papaverine	HP-β-CD	80	8	8.00
Papaverine(+)	HP-β-CD	10	10	
Papaverine	$(SBE)_{7M}$-β-CD	725	68	1.27
Papaverine(+)	$(SBE)_{7M}$-β-CD	570	51	

[a] The derived K_c values are the averages of two experiments.

viewed as a ternary system, with the interior cavity of cyclodextrin being the "non-polar solvent", and water being the polar solvent. Thus, molecules that cannot interact effectively with water tend to interact well with the apolar solvent (cyclodextrin cavity) and vice versa (23,24), assuming the geometry is favorable. This effect is observed with the decrease in K_c of molecules complexing to the HP-β-CD upon ionization. However, the larger decreases in complexation of the negatively charged molecules binding to $(SBE)_{7M}$-β-CD compared to the same complexes of HP-β-CD suggests the existence of an additional ionic repulsion force between the charged sulfonates and the negative guest molecules. Conversely, in cases where the guest molecules possess a positive charge, electrostatic attraction may occur between the positive charge of the guest and the negative sulfonates of the $(SBE)_{7M}$-β-CD. The presence of this charge attraction seems to counter balance the adverse effect of the increased substrate hydrophilicity discussed earlier, thus maintaining their binding potential (see Table IV).

Effect of Ionic Strength on Complexation of Charged Molecules

To further investigate the effect of charge interaction, K_c values of charged substrates were determined in solutions of varying ionic strength. The effect of increasing ionic strength on complexation of anionically charged molecules such as naproxen to HP-β-CD and $(SBE)_{7M}$-β-CD is shown in Figure 2a. Negatively charged molecules display a stronger complexation to HP-β-CD than $(SBE)_{7M}$-β-CD. Both modified cyclodextrins showed improved binding ability with an increase in the ionic strength of the solution, however, this increase was more pronounced with $(SBE)_{7M}$-β-CD than HP-β-CD. The increased K_c values upon increasing ionic strength suggest reduction in charge-charge repulsion due to charge shielding at higher solution ionic strengths. The effect of ionic strength on cationic molecules such as prazosin interacting with HP-β-CD and $(SBE)_{7M}$-β-CD is shown in Figure 2b. In

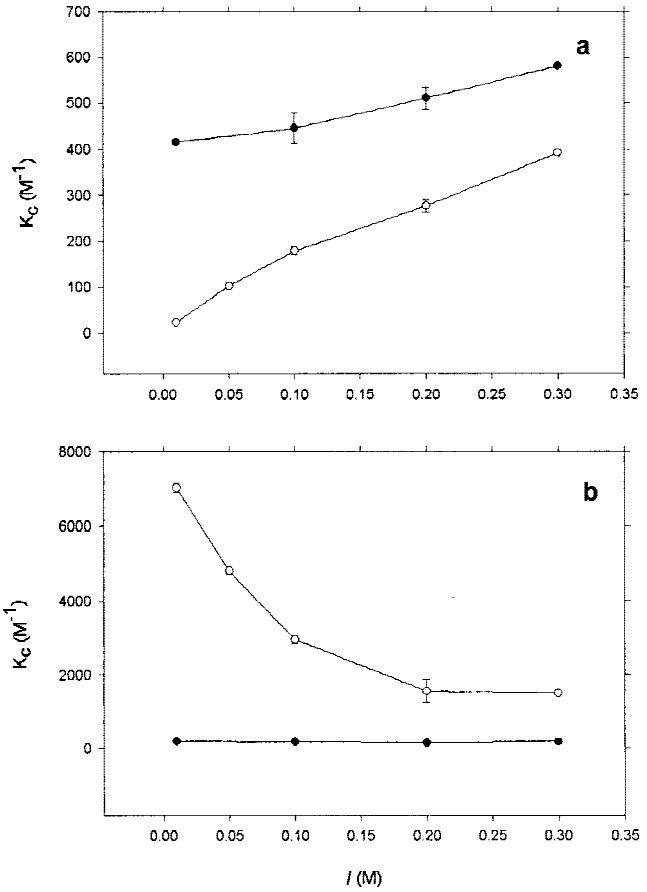

Fig. 2. A representative example of the effect of ionic strength on the complexation of (**a**) negatively charged substrate (naproxen in this case) and (**b**) positively charged substrate (prazosin in this case) to HP-β-CD (●) and $(SBE)_{7M}$-β-CD (○), at 25°C and using NaCl to control ionic strength. The results are the average of two experiments with the error bars representing the upper and lower limits (in some cases the error bars are small enough to be within the symbols).

contrast to the effects seen with negatively charged molecules, the binding of cationic molecules to $(SBE)_{7M}$-β-CD decreases with an increase in the solution ionic strength, and approaches the K_c value seen for HP-β-CD. In such cases, the charge shielding is also evident as a reduction in K_c value of positively charged molecules complexing to negatively charged cyclodextrin at higher solution ionic strength. Unfortunately, the K_c of HP-β-CD/papaverine was too small to be determined accurately by our method. An increase in the solution ionic strength generally weakens ion-ion and ion-dipole interactions (25). The fact that the complexation of charged molecules to negatively charged $(SBE)_{7M}$-β-CD are highly dependent on the solution electrolyte concentration verifies the significance of charge interactions in stabilizing or destabilizing a complex.

Figure 3 shows the plots of log-K_c versus the square root of ionic strength ($I^{1/2}$) for anionic and cationic molecules binding to HP-β-CD and $(SBE)_{7M}$-β-CD. Such plots may allow one to determine K_c values independent of salt effect by extrapolation to zero ionic strength (16,26). Figures 3a and 3b represent the complexation of all neutral and charged molecules with HP-β-CD and $(SBE)_{7M}$-β-CD, respectively. Neutral molecules binding to either cyclodextrin in Figure 3a dis-

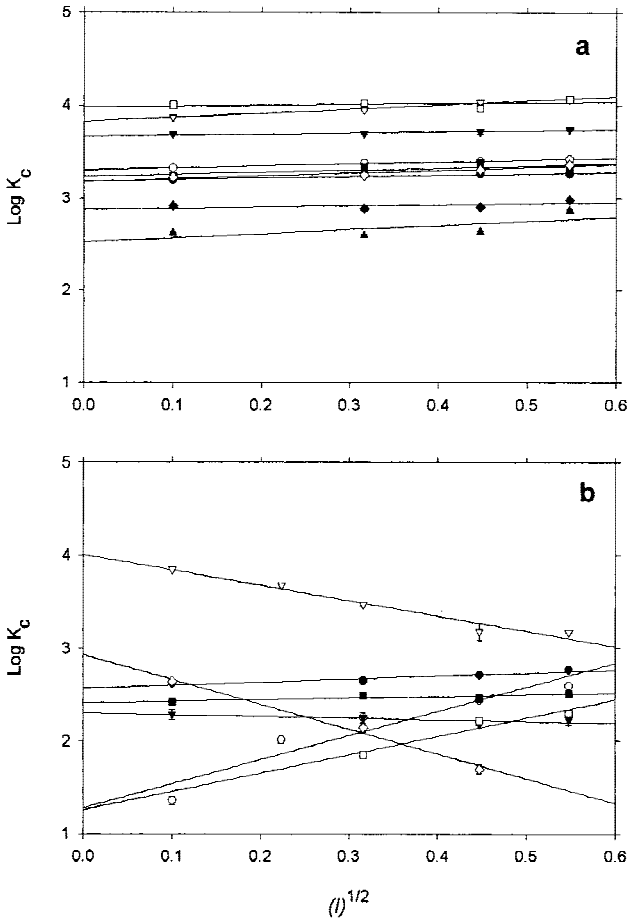

Fig. 3. Log K_c versus square root of ionic strength ($I^{1/2}$) for various compounds forming inclusion complexes with HP-β-CD (closed symbols) and $(SBE)_{7M}$-β-CD (open symbols); **a**) complexation of neutral molecules to the cyclodextrins. Hydrocortisone (○,●); Naproxen (▼,▲); Prazosin (■,□); Warfarin (♦,◇); Papaverine (▲); **b**) complexation of charged molecules to cyclodextrins. Naproxen (○,●); Prazosin (▼,▽); Warfarin (■,□); Papaverine (♦,◇). The results are the average of two experiments with the error bars representing the upper and lower limits (in some cases the error bars are small enough to be within the symbols).

play relatively small slopes, signifying the lack of charge influences in complex formation. However, charged molecules binding to the charged cyclodextrin ($(SBE)_{7M}$-β-CD) in Figure 3b display plots with steeper slopes compared to HP-β-CD, once again implying the more significant role of charged in the substrate/$(SBE)_{7M}$-β-CD interaction. The extrapolation of the linear fits to the intercept gives the apparent K_c at zero ionic strength, where the effect of charge is greatest. As shown in Table V, the K_c of anionic warfarin and naproxen are 14 and 20 times stronger with HP-β-CD than $(SBE)_{7M}$-β-CD, re-emphasizing the effect of charge-charge repulsion between a negatively charged substrate and $(SBE)_{7M}$-β-CD. The complexation of positively charged prazosin (Table V) at zero ionic strength is about 50 time greater with $(SBE)_{7M}$-β-CD than HP-β-CD, suggesting strong opposite charge attraction forces between the host $(SBE)_{7M}$-β-CD and the cationic guest molecule.

Based on the Debye-Hückel description of charge interactions, the changing K_c as a function of ionic strength in an aqueous solution may be derived from the equilibrium reaction in scheme 1 (27–30). The intrinsic K_c (K_c^0) is the product of the concentration (c) and activity coefficient (γ) dependent equilibriums (Eqs. 1 and 2) (13), which may be written in logarithmic terms (Eq. 3).

$$S + C \rightleftarrows S \cdot CD \qquad \text{Scheme 1}$$

$$K_c^0 = \frac{a_{SCD}}{a_S a_{CD}} = \frac{c_{SCD}}{c_S c_{CD}} \cdot \frac{\gamma_{SCD}}{\gamma_S \gamma_{CD}} \tag{1}$$

$$K_c^0 = K_c K_\gamma \tag{2}$$

$$\log K_c = \log K_c^0 - \log\left(\frac{\gamma_{SCD}}{\gamma_S \gamma_{CD}}\right) \tag{3}$$

The γ of an ionic species i can be derived from Eq. 4, where A is a solvent dependent constant and z is the charge valence of an ion I (27). For water at 25°C, A is 0.5091.

$$\log \gamma_i = -A z_i^2 \tag{4}$$

The Debye-Hückel equation may be combined with the equilibrium equation (Eq. 1) to give Eq. 5, up to a limit of 0.1 M ionic strength (27), or Eq. 6 up to a limit of 0.5 M ionic strength (27).

$$\log K_c = \log K_c^0 + 2 A z_+ z_- \sqrt{I} \tag{5}$$

$$\log K_c = \log K_c^0 + \frac{2 A z_+ z_- \sqrt{I}}{(1 + \sqrt{I})} \tag{6}$$

The term $2Az_+z_-$ comes from $z_\pm^2 = (z_+ + z_-)^2$ which may be reduced to $-2Az_+z_-$. Thus, a plot of log K_c versus $I^{(1/2)}$ should produce a straight line with the slope and intercept of $-2Az_+z_-$ and $\log K_c^0$, respectively. Since the z values are algebraic numbers, the plot for two molecules with opposite charges will have a negative slope, and a plot for two mol-

Table V. The Slope and Intercept Values Corresponding to Fig. 4, Determined from Linear Plots of Log K_c vs. Ionic Strength for the Binding of Positive and Negative Molecules to HP-β-CD and $(SBE)_{7M}$-β-CD

	HP-β-CD			$(SBE)_{7M}$-β-CD			
Substrate	Slope	Intercept	R^2	Slope	Intercept	R^2	$K_{I\rightarrow 0\ Ratio}$[a]
Naproxen(−)	0.322	2.571	0.91	2.590	1.284	0.91	20
Warfarin(−)	0.168	2.413	0.71	1.972	1.262	0.92	14
Prazosin(+)	−0.167	2.300	0.59	−1.643	4.010	0.96	0.02
Papaverine(+)	ND	ND	ND	−2.674	2.931	0.99	ND

[a] Ratio of HP-β-CD to $(SBE)_{7M}$-β-CD at ionic strength approaching zero.

ecules with similar charges should display a positive slope (29,30).

Assuming the charge interaction occurring in this case follows the spherical cavity model, one may theoretically calculate the number of ionic bridging in the system (27,28). For example, for the $(SBE)_{7M}$-β-CD/substrate complex, assuming that all seven sulfonates were involved in charge interaction with the positive charge of the substrate, one would expect a slope of –6.11 ($z_{CD} = -7$, $z_s = +1$, $z_{CDS} = -6$).

In the case of prazosin and papaverine the slopes are –1.6 and –2.7, respectively (see Table V), suggesting an average of 1.8 and 2.3 units of negatively charged sulfonates (roughly 2 units) interact with the positively charged substrates studied. Therefore, approximately an average of two sulfonate moieties of $(SBE)_{7M}$-β-CD interact with the positive charge of the guest molecule in forming the complex. Similar interaction of 2.0 and 2.5, although of charge-charge repulsion type is seen with warfarin and naproxen, respectively. Interestingly, the similarity of warfarin (2.0) and prazosin (1.8) in electrostatic attraction and repulsion may be related to their structure, having their charge buried within their molecular structure. In the case of papaverine and naproxen, where their charge is more removed from the hydrophobic part of the molecule, there seems to be a stronger electrostatic interaction of 2.3 and 2.5 units. Further studies are necessary in determining the underlying principle for the above observation.

CONCLUSION

$(SBE)_{7M}$-β-CD displayed a larger binding capability compared to HP-β-CD in forming inclusion complexes with neutral substrates. Charged molecules (cationic or anionic) binding to neutral cyclodextrin, HP-β-CD, displayed a decrease (2 to 31 times) in complexation, compared to their neutral counterparts. The presence of a negative charge on the substrate reduced its complexation to $(SBE)_{7M}$-β-CD by about 40 times, which was attributed to ionic repulsion effects. Positively charged substrates complexing to $(SBE)_{7M}$-β-CD did not display much change in binding strength when compared to their neutral counterparts, due to opposite charge interactions of the substrate and sulfonate moieties of $(SBE)_{7M}$-β-CD. Due to the presence of charge-charge interaction, it was shown that the complexation strengths of molecules may be manipulated through solution electrolyte concentrations. Further analysis suggested that the ionic interaction of the charged substrates studied occurred through interactions with up to two sulfonate groups of the $(SBE)_{7M}$-β-CD.

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