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Talanta 68 (2006) 1574–1583
Talanta
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Determination of enantiomeric composition of samples by multivariate regression modeling of spectral data obtained with cyclodextrin guest–host complexes—Effect of an achiral surfactant and use of mixed cyclodextrins

Sayo O. Fakayode, Marianna A. Busch, Kenneth W. Busch *

Department of Chemistry & Biochemistry, Baylor University, One Bear Place #97348, Waco, TX 76798, USA

Received 27 May 2005; received in revised form 6 August 2005; accepted 6 August 2005
Available online 28 September 2005

Abstract

The determination of the enantiomeric composition of samples by chemometric modeling of spectral data was investigated for samples of *N*,*N*′-bis-(α-methylbenzyl) sulfamide and tryptophan methyl ester hydrochloride. Multivariate regression models (PLS-1) were developed from spectral data obtained on solutions containing *N*,*N*′-bis-(α-methylbenzyl)sulfamide or tryptophan methyl ester hydrochloride in the presence of sodium dodecyl sulfate and mixed cyclodextrin host molecules. The regression models were subsequently used to predict the enantiomeric composition of laboratory-prepared test samples of *N*,*N*′-bis(α-methylbenzyl)sulfamide or tryptophan methyl ester hydrochloride. The capability of the models to accurately predict the enantiomeric composition was evaluated in terms of the root-mean-square percent relative error (RMS %R.E.) as calculated from the results obtained with independently prepared validation sets of samples. It was found that the presence of SDS in most cases either had little effect on the predictive ability of the model or it actually reduced the predictive ability of the model. Moreover, it was found that the use of mixed CDs, either in the presence or absence of SDS, reduced the predictive ability of the regression model when compared with results obtained with individual CDs.

Keywords: Chiral analysis; Multivariate regression modelling; Cyclodextrin guest–host inclusion complexation; Sodium dodecyl sulfate surfactant

1. Introduction

The determination of the enantiomeric composition of chiral samples is of considerable interest in the pharmaceutical industry because of wide differences in the pharmacological and physiological properties of enantiomers. Thus, while one enantiomer of a chiral molecule may be therapeutically active, the other enantiomer may not only be therapeutically inactive, but may also have pronounced toxic effects [1–3].

Chiral analysis is traditionally carried out by chiroptical methods such as polarimetry [4], Raman optical activity [5], and electronic and vibrational circular dichroism [6,7] where the stereogenic center of the chiral molecules interacts with polarized light. Separation methods using chromatography or capillary electrophoresis for chiral analysis are also widely used [8–10].

Chiral analysis with non-chiroptical methods requires some form of a chiral auxiliary [11,12], which interacts with the enantiomeric pair to break the mirror-image symmetry by formation of diastereomeric products. For effective enantiomeric differentiation, the interaction must occur between the stereogenic center of the chiral molecules and the chiral center of the chiral auxiliary. Cyclodextrins (CDs) are homochiral barrel-shaped macrocyclic sugar molecules that have been widely used as chiral auxiliaries because of the capability of CDs to form transient, non-covalent, diastereomeric guest–host inclusion complexes with various guests [13–16].

Recent studies in our laboratory [17–20] have demonstrated that the enantiomeric composition of various chiral guest molecules can be determined with reasonable accuracy by multivariate regression modeling of spectral data obtained from solutions containing cyclodextrin as a chiral auxiliary. The premise behind the approach is that inclusion complex formation between the chiral guest analyte and the homochiral CD host results in the formation of transient diastereomeric inclusion complexes with different physical and spectral properties.

* Corresponding author.
E-mail address: Kenneth_Busch@baylor.edu (K.W. Busch).

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doi:10.1016/j.talanta.2005.08.018

As a result, it is observed that, for solutions containing a fixed chiral guest concentration and a fixed CD host concentration, the absorption or emission spectra vary slightly as the enantiomeric composition of the samples is changed. The small spectral changes are then correlated with the known enantiomeric composition of the guest analyte using standard multivariate regression modeling techniques such as partial-least-squares regression (PLS-1) [21–25].

Previous studies using this technique [17–20] have revealed that the prediction accuracy obtained by means of multivariate regression modeling of spectral data depends on the particular cyclodextrin used with a given chiral analyte. In this study, we investigate whether this problem can be solved by the use of a chiral auxiliary containing a mixture of cyclodextrins. The premise behind this portion of the study is that in a mixture of cyclodextrins the chiral guest molecule will have the opportunity to interact with a variety of cyclodextrins and may interact preferentially with the one that would give the optimum regression model when used singly.

Another problem encountered with our previous studies is the limited solubility of large chiral molecules of pharmaceutical interest in aqueous media. The solubility of hydrophobic organic molecules in aqueous media can often be improved by the use of an organic solvent modifier such as a surfactant. Surfactants, or surface-active agents, are particularly useful for solubilizing hydrophobic compounds because they are amphiphilic materials containing both apolar long-chain hydrocarbon "tails" and polar "head" groups. Indeed, the unique properties of surfactants have made them very popular in micellar electrokinetic chromatography [26–29], and the use of surfactants in combination with cyclodextrins for chiral analysis has recently been reported [30,31].

In this study, the determination of the enantiomeric composition of the highly hydrophobic guests, *N*,*N*′-bis(α-methylbenzyl)sulfamide and tryptophan methyl ester hydrochloride, was carried out by multivariate regression modeling of UV–vis absorption spectra of CD guest–host inclusion complexes. Furthermore, the influence of sodium dodecyl sulfate surfactant on the CD guest–host inclusion complexation and the use of mixed CD host molecules were investigated.

2. Experimental

Enantiomerically pure (*S*,*S*)-(−)-*N*,*N*′-bis(α-methylbenzyl) sulfamide (*S*,*S*-BMBS), (*R*,*R*)-(+)-*N*,*N*′-bis(α-methylbenzyl) sulfamide (*R*,*R*-BMBS), D-tryptophan methyl ester hydrochloride (D-TME), and L-tryptophan methyl ester hydrochloride (L-TME), sodium dodecyl sulfate surfactant (SDS), beta-cyclodextrin (β-CD), gamma-cyclodextrin (γ-CD), methyl-β-cyclodextrin (Me-β-CD), and hydroxypropyl-β-cyclodextrin (HP-β-CD) were obtained from Aldrich Chemical Company and used as received.

Stock solutions of CDs were prepared in deionized water or in water/ethanol mixtures (3:2) in the presence or absence of SDS surfactant. Stock solutions of BMBS and TME enantiomers were prepared by weighing appropriate amounts of the two enantiomeric forms of BMBS or TME and dissolving them in the stock CD solution. In all cases, preparation of solutions involving SDS surfactant was made slowly to avoid excessive foaming of the surfactant. For a given experiment, all solutions contained a fixed CD concentration and a fixed guest concentration. The enantiomeric composition of the calibration samples was varied from mol fraction 0.100 to 0.900 of (*S*,*S*)-BMBS or D-TME.

The spectra of the solutions were recorded with a Hewlett-Packard photodiode array (Model 8455) UV–vis spectrophotometer using a 1.0-cm path length quartz cell over the wavelength range from 190 to 1100 nm.

The mean-centered spectral data were subjected to multivariate analysis using a commercial chemometric software package obtained from CAMO Inc. (The Unscrambler 8.0). Partial-least-squares regression was performed on the spectral data using full cross-validation (leave-one-out validation).

3. Results and discussion

3.1. Studies with *N*,*N*′-bis(α-methylbenzyl)sulfamide

The molecular structures of BMBS and TME are shown in Fig. 1. BMBS is highly hydrophobic with poor solubility in water or in ordinary aqueous CD solutions. Indeed, the dissolution of BMBS was only achieved in a water/ethanol mixture (3:2) containing CD in combination with SDS surfactant. SDS is an achiral anionic surfactant usually used to improve the solubility of hydrophobic molecules either in combination with CDs or other organic solvent modifiers. SDS in water has a critical micelle concentration (CMC) of 8 mM; however, SDS solutions may have lower CMC values in the presence of additives or when used in combination with other materials [32]. At concentrations above the CMC, micelles are formed, which can effectively solubilize highly hydrophobic guests such as BMBS.

Fig. 2A shows the UV absorption spectra obtained for solutions containing a fixed Me-β-CD concentration (7.5 mM) and a fixed BMBS concentration (3.75 mM) of varying enantiomeric composition in the presence of SDS surfactant (10 mM). Although the BMBS concentration and the Me-β-CD concentration are both fixed, the spectra vary with enantiomeric composition. Fig. 2B shows an expanded view of the spectra over the wavelength region between 244 and 255 nm where the spectra vary most with enantiomeric composition of BMBS. Close inspection of Fig. 2B reveals several points where the spectra of solutions with different enantiomeric composition cross. Additionally, the spectra are not in order indicating the spectral variations are not just an offset from each other. The variations of spectra with enantiomeric composition shown in Fig. 2 are consistent with our previous findings reported elsewhere [17–20].

Fig. 2C shows a plot of the mean-centered spectral data obtained with solutions containing BMBS and Me-β-CD in the presence of SDS surfactant. This plot was obtained by averaging the spectra of the eight calibration samples, and subtracting this average spectrum from each individual spectrum on a wavelength-by-wavelength basis [20]. The average spectrum was computed by adding the absorbances of the individual spectra on a wavelength-by-wavelength basis and dividing the sum

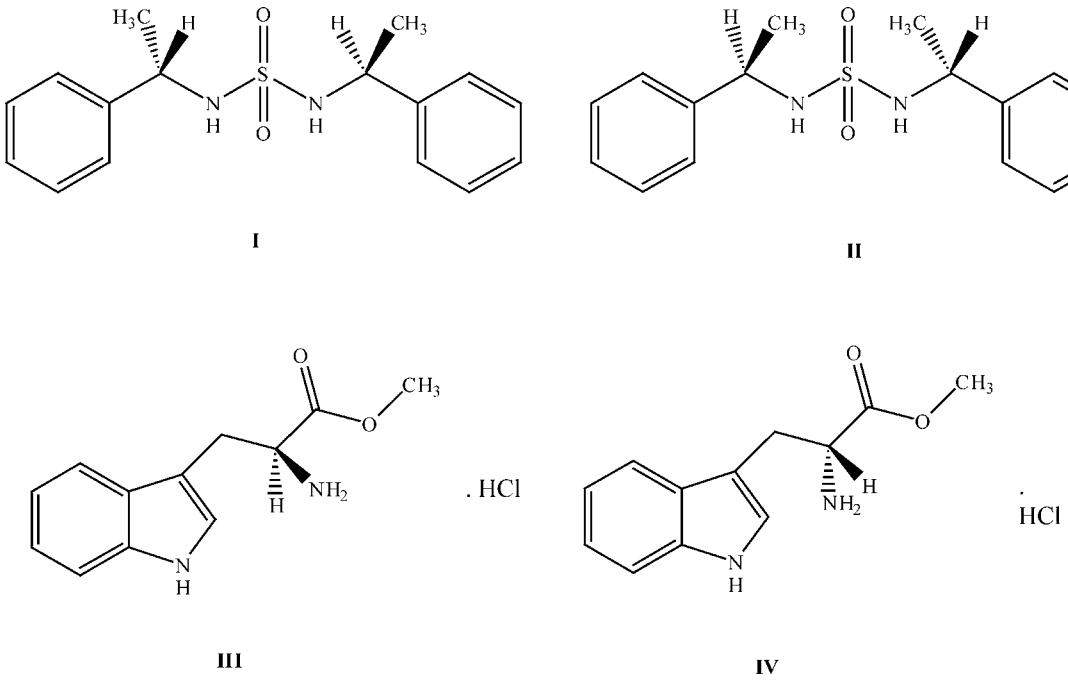

Fig. 1. Molecular structure of chiral analyte guests and sodium dodecyl sulfate surfactant: (**I**) (*S*,*S*)-(−)-*N*,*N*′-bis(α-methylbenzyl)sulfamide; (**II**) (*R*,*R*)-(+)-*N*,*N*′-bis(α-methylbenzyl)sulfamide; (**III**) L-tryptophan methyl ester hydrochloride; (**IV**) D-tryptophan methyl ester hydrochloride.

for each wavelength by the number of spectra. Plots of the mean-centered spectra reveal the spectral changes that occur with enantiomeric composition more clearly and once again reveal that the curves do not follow a particular order with respect to enantiomeric composition. It is because of this lack of order that univariate techniques will not work and multivariate regression modeling must be used.

The use of multivariate regression modeling for correlation of small spectral variations with known compositional changes has been well established in chemistry [21–25]. The details of the use of PLS-regression modeling of spectral data for the determination of enantiomeric composition have been previously described elsewhere [17–20]. In brief, multivariate regression modeling is a two-phase process. In the first, or calibration, phase, a regression model is developed from the spectral data obtained with a training set of samples whose enantiomeric composition is known independently (the enantiomeric composition BMBS or TME in this study). In the second, or validation, phase, the enantiomeric composition of a laboratory-prepared test set of solutions (the validation set) is predicted from its spectral data using the regression model developed in the calibration phase.

The summary of the results of regression modeling of BMBS and Me-β-CD guest–host complexes in the presence of SDS surfactant is shown in Fig. 3. In PLS regression modeling, a new, more optimal, dimensionality-reduced coordinate system is developed from the data [21–25]. The eigenvectors that make up the new coordinate system are known as PLS components. When the samples are plotted on the new coordinate system, the result is known as a scores plot. Scores plots are often useful because they can often reveal relationships among samples.

Fig. 3A shows a two-dimensional PLS-scores plot of the first PLS component (PLS_1, abscissa) versus the second PLS component (PLS_2, ordinate). The numbers in the plot are the sample numbers of the calibration set. Sample number 7 was identified as an outlier and was not use for the regression analysis. As shown in the figure, the first PLS component explained 97% of the total variation in the spectral data along with 28% of the total variance in enantiomeric composition of the BMBS calibration samples. The second PLS component explained the remaining 3% of the spectral variation and an additional 33% of the variance in the enantiomeric composition of the BMBS calibration samples.

Fig. 3B is the plot of the regression coefficients versus wavelength. These coefficients make up the regression model that relates the predicted enantiomeric composition of a given sample to its measured absorption spectrum (i.e., the absorbances at wavelengths 1 to *n*) [19]. In mathematical terms, this relationship can be expressed as

$$\hat{y} = b_0 + b_1 A_1 + b_2 A_2 + \cdots + b_n A_n \quad (1)$$

where $\hat{y}$ is the predicted enantiomeric composition of a sample whose spectrum is made up of the measured absorbances over the spectral interval from wavelengths 1 to *n*. The regression coefficients that result from PLS modeling are the *b*-values in Eq. (1). Fig. 3B shows that the plot of the regression coefficients versus wavelength is approximately sinusoidal with some wavelengths contributing positively to the regression model while others contribute negatively to the model.

Fig. 3C is the plot of the predicted enantiomeric composition of BMBS by the PLS-1 regression model versus the known laboratory-prepared enantiomeric compositions of BMBS calibration samples. The correlation coefficient, the slope, and the offset obtained from the plot of the predicted enantiomeric composition versus the known enantiomeric composition in Fig. 3C

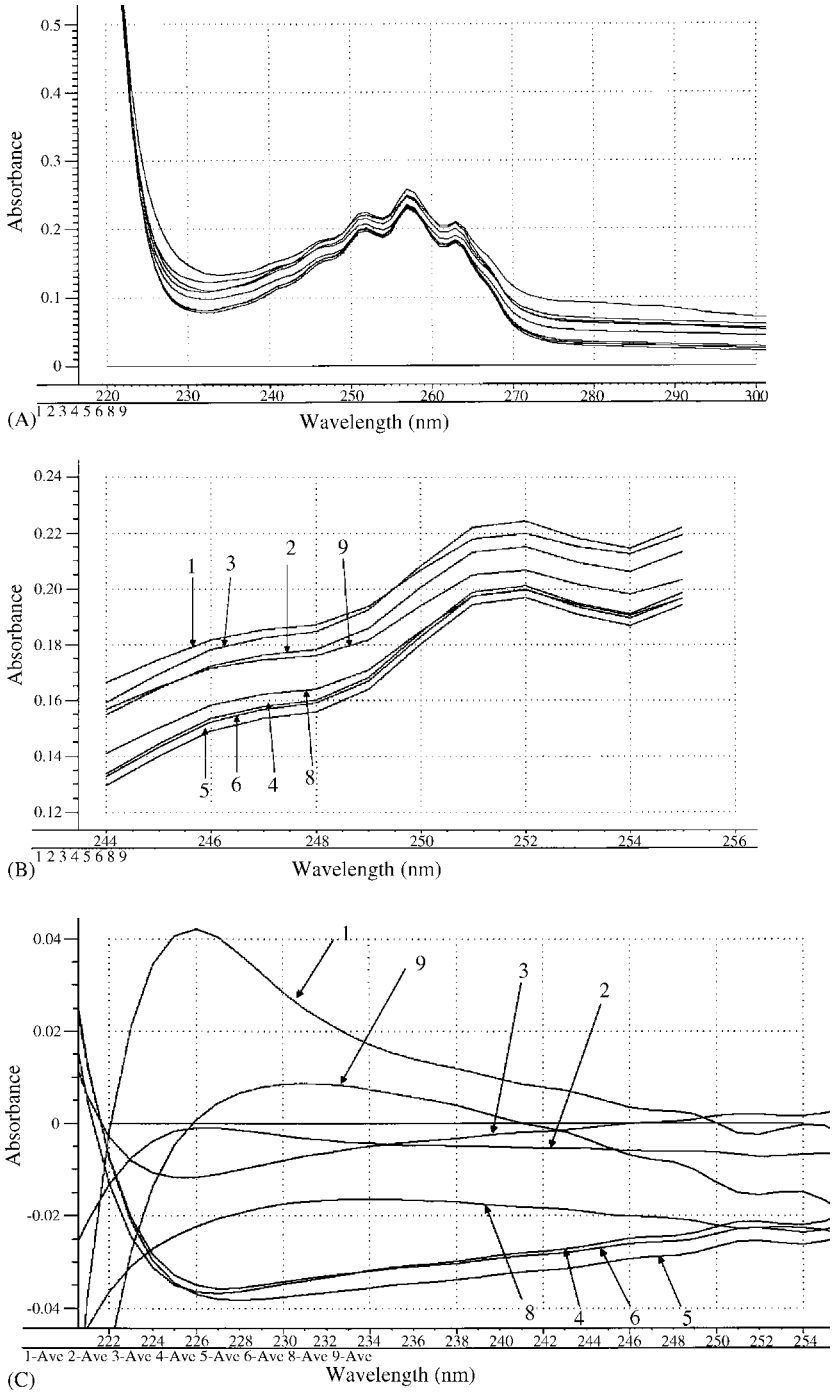

Fig. 2. Absorption spectra of BMBS and Me-β-CD complexes: (A) nine solutions containing 7.5 mM Me-β-CD S and 3.75 mM BMBS of varying enantiomeric compositions in the presence of 10 mM SDS; (B) Expanded spectrum showing solutions of varying enantiomeric composition: (1) 0.100; (2) 0.200; (3) 0.340; (4) 0.400; (5) 0.500; (6) 0.600; (8) 0.800; (9) 0.900 mol fraction (*S*,*S*)-(−)-BMBS; (C) mean-centered spectra of calibration samples: (1) 0.100; (2) 0.200; (3) 0.340; (4) 0.400; (5) 0.500; (6) 0.600; (8) 0.800; (9) 0.900 mol fraction of (*S*,*S*)-BMBS.

were 0.9998, 0.9996, and 6.77×10^{-7}, respectively. A perfect model would have a correlation coefficient of 1, a slope of 1, and an offset of 0.

To test the influence of different CD hosts on the quality of the regression model, similar studies were carried out for BMBS using various CD hosts in the presence of 10 mM SDS surfactant. Two native CDs (β-CD and γ-CD) and two modified CDs (Me-β-CD and HP-β-CD) were selected to study the influence of cavity size and rim substitution on the predictive abilities of the regression models. Table 1 shows the figures of merit obtained for the PLS-1 regression models obtained using various CD hosts.

While the figures of merit shown in Table 1 for the regression models obtained with various CD hosts are quite good,

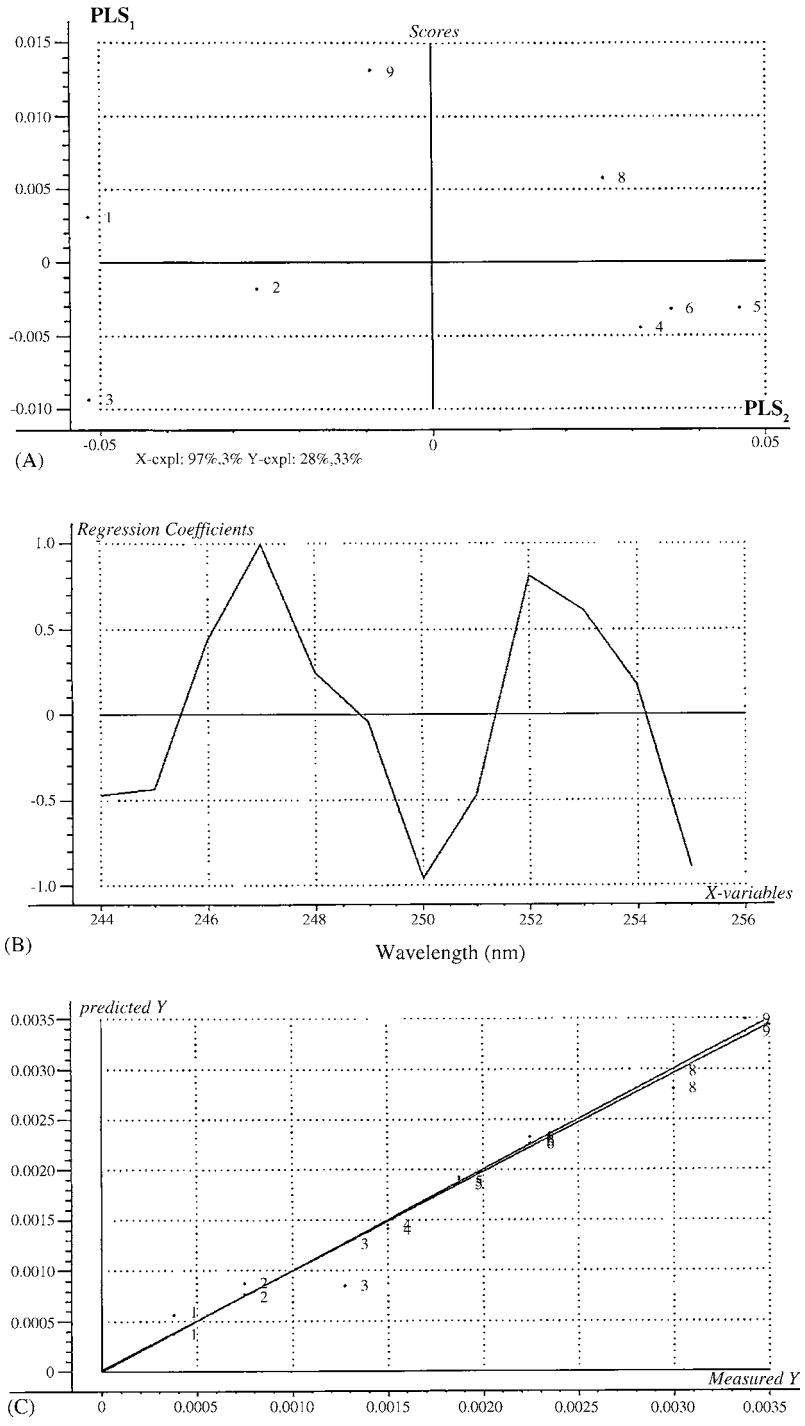

Fig. 3. Summary of regression results obtained with solutions containing (*S*,*S*)-BMBS and Me-β-CD complexes: (A) scores plot; (B) regression coefficients as a function of wavelength; (C) plot of predicted *Y*-values vs. known *Y*-values.

the real test of any regression model is its ability to accurately predict the enantiomeric composition of future samples. To evaluate the performance and prediction capabilities of the model, a set of eight validation samples containing a fixed Me-β-CD concentration and a fixed BMBS concentration of varying enantiomeric composition in the presence of SDS surfactant was prepared. The absorption spectra of the validation samples were recorded over the same wavelength range used for the calibration samples and the enantiomeric compositions of the validation samples were predicted from the spectral data using the regression model developed in the calibration stage. It should be noted that although the total BMBS concentration in the calibration and validation samples was the same, the validation samples had different enantiomeric compositions from those used to prepare the model in the calibration phase.

The ability of the regression model to accurately predict the enantiomeric composition of the validation samples was evaluated by calculating the root-mean-square percent relative error

Table 1
Summary of figures of merit for regression models made for *N*,*N*′-bis(α-methylbenzyl)sulfamide with various cyclodextrin host molecules in the presence of sodium dodecyl sulfate surfactant

Host molecule	Correlation coefficient	Slope	Offset	Number of PCs used	Wavelength range (nm)
SDS + β-CD[a]	0.9990	0.9979	3.69×10^{-6}	5	234–250
SDS + γ-CD[b]	0.9998	0.9997	5.81×10^{-7}	5	219–290
SDS + Me-β-CD[c]	0.9998	0.9996	6.77×10^{-7}	5	245–256
SDS + HP-β-CD[d]	0.9906	0.9813	3.54×10^{-5}	5	225–256

[a] 10 mM SDS, 7.5 mM β-CD and 3.75 mM *N*,*N*′-BMBS.
[b] 10 mM SDS, 7.5 mM γ-CD, and 3.75 mM *N*,*N*′-BMBS.
[c] 10 mM SDS, 7.5 mM Me-β-CD and 3.75 mM *N*,*N*′-BMBS.
[d] 10 mM SDS, 7.5 mM HP-β-CD and 3.75 mM *N*,*N*′-BMBS.

(RMS %R.E.) given by

$$\text{RMS \%R.E.} = \sqrt{\frac{\sum (\text{RE}_i)^2}{n}} \quad (2)$$

where RE_i is the relative error for the *i*th sample, and *n* is the number of samples in the test set.

The results of the validation studies for BMBS are shown in Table 2. In agreement with our previous studies [17–20], the predictive ability of the regression models for BMBS was found to be highly dependent on the particular host CD molecule used. This is not surprising since enantiomeric discrimination is expected to depend on the extent of diastereomeric interactions between the chiral guest and the chiral auxiliary host. Whatever the exact nature of these diastereomeric interactions, it is not unreasonable to suppose that they will depend, to a large degree, on the extent of inclusion complex formation.

Since BMBS is highly hydrophobic, it might be expected that it would prefer to leave the hostile aqueous medium to enter the more compatible hydrophobic environment of the CD cavity, making inclusion complex formation favorable. Moreover, the extent of guest–host inclusion complex formation with a particular CD might be expected to depend on the nature, size, and shape of the guest molecule as well as the ability of the host molecule to accommodate the guest, and better inclusion complexation would be expected when the guest is of the right dimension to properly fit into the CD cavity.

In comparing the results shown in Table 2, we see that the models made with the two native CDs gave unsatisfactory predictive abilities, although the model made with γ-CD gave better results than that obtained with β-CD. BMBS is a fairly large molecule with two phenyl groups and two chiral centers. As result, better inclusion complex formation (and hence a better predictive model) might be expected with γ-CD compared with β-CD in agreement with the results in Table 2.

Nevertheless, cavity size alone is not the only important factor determining the predictive ability of a given regression model with a particular CD host. In the case of native CDs, the role of hydrogen bonding may also be important. A major driving force in inclusion complex formation that is frequently cited [33,34] with native CDs is hydrogen bonding between the OH groups on the rim of the cavity and the guest molecule. In the study with BMBS, hydrogen bonding could conceivably play several roles.

With the native CDs, the OH groups on the cavity rim are readily available for hydrogen bonding with the oxygens on the sulfamide moiety of BMBS. If this hydrogen bonding forces the stereogenic center of the guest molecule into the CD cavity, it could improve the predictive ability of the model by enhancing diastereomeric effects. On the other hand, if hydrogen bonding of BMBS causes it to perch on the rim of the CD without entering the cavity, the stereogenic center may not experience the chiral environment of the cavity interior and diastereomeric effects may be reduced with a concomitant loss in predictive ability of the model.

Table 2
Relative errors obtained for (*S*,*S*)-(−)-*N*,*N*′-bis(α-methylbenzyl)sulfamide with different cyclodextrin host molecules in the presence of sodium dodecyl sulfate surfactant

Actual mol fraction	SDS + β-CD		SDS + γ-CD		SDS + Me-β-CD		SDS + HP-β-CD	
	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.
0.328	0.762	132	0.518	58	0.352	7.3	0.616	87.8
0.452	0.555	22.8	0.608	34.5	0.494	9.3	0.733	62.2
0.548	0.615	12	0.663	21.0	0.493	−10	0.596	8.8
0.620	0.610	−2	0.666	7.4	0.594	−4.2	0.699	13
0.715	0.712	−0.4	0.800	12	0.698	−2.4	0.917	28.3
0.752	0.965	28.3	0.510	−32.2	0.763	1.5	0.688	−8.5
0.844	1.300	54.0	0.804	−5	0.811	−3.9	1.290	52.8
0.892	0.886	−0.7	0.963	8.0	0.856	−4.0	1.330	49.1
RMS %R.E.		52.2		28.1		6.1		47.3

Alternatively, hydrogen bonding could also occur with the oxygens on the sulfate moiety of the SDS surfactant. If this occurred, the non-polar dodecyl group might enter the CD cavity and compete with the intended BMBS guest molecules. Indeed, it may be possible for several SDS molecules to complex simultaneously with the unmodified CDs. If such competition occurred, poor predictive models might result because the chiral analyte would not be able to interact with the chiral auxiliary.

Finally, the SDS surfactant could compete directly with cyclodextrin for BMBS. In the experiments with BMBS, the SDS concentration was 10 mM, which is above the critical micelle concentration. If micelles are indeed present in the solution, the interior of the micelle (made up of dodecyl chains) will be hydrophobic and might provide an alternative hydrophobic environment for BMBS. If this were to occur, the extent of inclusion complex formation with CD would go down, and the predictive ability of the model would be adversely affected.

In examining the results obtained with the two modified CDs, we see that Me-β-CD gave a model with satisfactory predictive ability (RMS %R.E. of 6.1%) while HP-β-CD gave a model with unsatisfactory predictive ability (RMS %R.E. of 47.3%). In the case of Me-β-CD, the improvement in the predictive ability of the model over that obtained with β-CD may be attributed to reduced hydrogen bonding between the SDS surfactant and Me-β-CD or reduced hydrogen bonding between BMBS and Me-β-CD. In contrast to the results obtained with Me-β-CD, the predictive ability of the model made with HP-β-CD is relatively poor (RMS %R.E. 47%). This may be due to the size of the substituent moiety group on the rim of the CD cavity or the possible adverse effect of hydrogen bonding with the hydroxypropyl groups on the rim of the cavity, preventing the BMBS guest from entering. In the case of HP-β-CD, the bulky hydroxypropyl group may cause steric hindrance that prevents easy penetration of large molecules such as BMBS into the HP-β-CD cavity.

The predictive ability obtained with Me-β-CD is in line with our previous study [19] with modified CDs in the absence of surfactants, where Me-β-CD gave models with norepinephrine and norephedrine having RMS %R.E. values of 3% and 6%, respectively. The comparable result obtained in this study might suggest that, in the case of Me-β-CD, the SDS surfactant is not playing a major role in chiral discrimination aside from

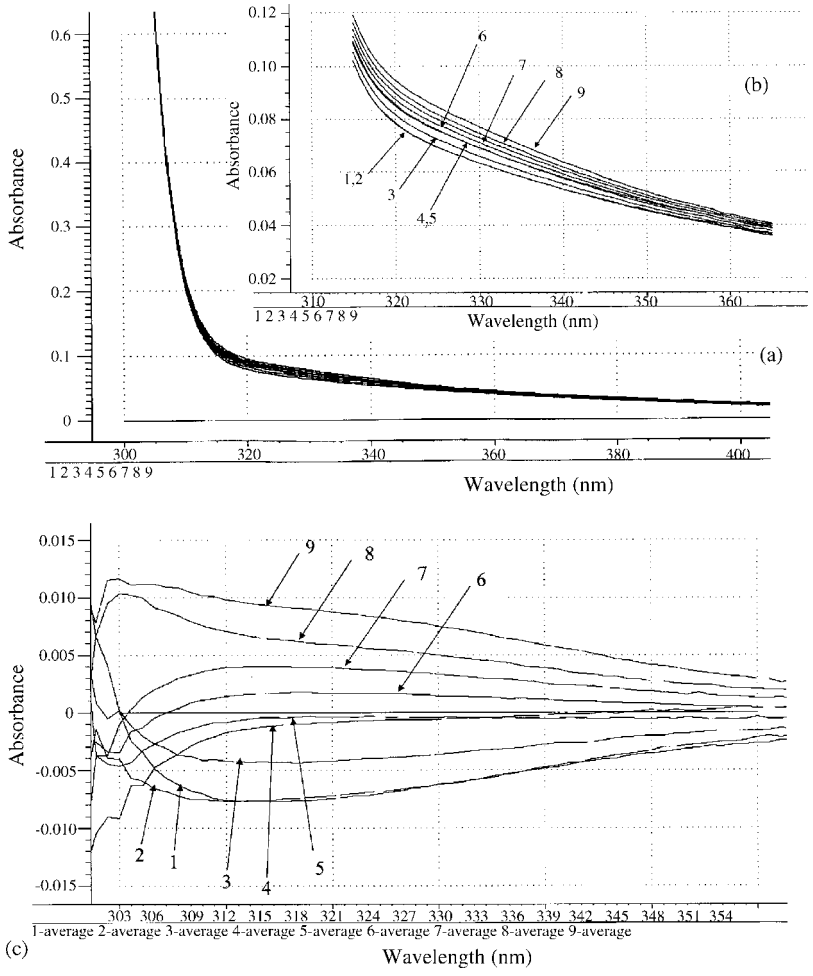

Fig. 4. Absorption spectra of nine solutions containing 7.5 mM HP-β-CD and 3.75 mM TME in the presence of 7.5 mM SDS. (a) Spectrum from 310 to 400 nm. (b) Expanded spectrum showing solutions of varying enantiomeric composition: (1) 0.100; (2) 0.200; (3) 0.340; (4) 0.400; (5) 0.500; (6) 0.600; (7) 0.700; (8) 0.800; (9) 0.900 mol fraction D-TME; (c) mean-centered spectra plot of calibration samples containing 7.5 mM of HP-β-CD and 3.75 mM TME vs. wavelength: (1) 0.100; (2) 0.200; (3) 0.340; (4) 0.400; (5) 0.500; (6) 0.600; (7) 0.700; (8) 0.800; (9) 0.900 mol fraction of D-TME.

acting as a solvent modifier, permitting the BMBS molecule to dissolve.

3.2. Studies with tryptophan methyl ester hydrochloride

Tryptophan methyl ester hydrochloride is the hydrochloride salt of the methyl ester of the amino acid tryptophan, where the α-amino group has a pK_a of 9.4 [35]. As a result, in solutions of TME with pH values less than 9, the α-amino group will be protonated and TME will be present in solution in a cationic form.

Fig. 4a shows the spectra of solutions containing 7.5 mM HP-β-CD and 3.75 mM of TME of varying enantiomeric composition in the presence of 7.5 mM SDS surfactant. Fig. 4b shows an expanded plot of these spectra over the wavelength range from 315 to 365 nm. Once again the spectra vary with enantiomeric composition even though the concentrations of HP-β-CD and TME are fixed. Fig. 4c shows a plot of the mean-centered spectra over the wavelength range from 300 to 357 nm. Using spectral data like that shown in Fig. 4, a series of regression models was prepared with TME using various combinations of hosts and surfactant. Table 3 gives the figures of merit for the regression models obtained with TME in this study.

3.2.1. Studies with individual cyclodextrins in the presence of surfactant

Table 4 shows the results obtained for the validation studies with TME and various CD hosts in the presence of 7.5 mM SDS surfactant. Once again, we see that for the native CDs, γ-CD (with the larger cavity) gives a model with better predictive ability than that obtained with a model based on β-CD. In general, the predictive values for the models made with TME and the native CDs were better by about a factor of two compared with those obtained with BMBS for the corresponding native CD hosts in the presence of SDS surfactant. In contrast to the results obtained with BMBS, in the case of TME, the best results (RMS %R.E. 5.7%) were obtained with HP-β-CD rather than with Me-β-CD as was the case with BMBS. The reason for this switch in model predictability is not clear. The only explanation that can be offered at this time is that, compared with BMBS, TME is less bulky; consequently, the steric hindrance of the hydroxypropyl groups of HP-β-CD on the TME/HP-β-CD guest–host interaction may be less pronounced.

For solutions with pH values less than 9, the α-amino group of TME will be protonated, and ion pairing between the cationic TME molecule and the anionic sulfate group of the surfactant may occur. The effect of any such ion pairing, if it occurs, on inclusion complexation with CD is not clear at this time. Since the concentration of SDS in the experiments with TME was 7.5 mM, micelle formation is not expected and any competition between the SDS surfactant and CD for TME may be less than that prevailing in the previous experiments with BMBS. This could explain why the RMS %R.E. values in Table 4 are somewhat better than those in Table 2.

In our previous study [19] with modified CDs in the absence of SDS surfactant, the best model for TME was obtained with carboxymethyl-α-CD (RMS %R.E. of 7%). In that study, Me-β-CD gave a model with TME with an RMS %R.E. value of 11% while HP-β-CD gave a corresponding model with an RMS %R.E. value of 18%. Comparing the results reported in the

Table 3
Summary of figures of merit for regression models made for tryptophan methyl ester hydrochloride with various host molecules

Host molecule	Correlation coefficient	Slope	Offset	Number of PCs used	Wavelength range (nm)
Mixed CDs					
γ-CD + Me-β-CD[a]	0.9994	0.9987	2.61×10^{-6}	5	321–340
γ-CD +HP-β-CD[b]	0.9824	0.9651	6.60×10^{-6}	5	310–330
Me-β-CD + HP-β-CD[c]	0.9107	0.9911	1.01×10^{-5}	5	320–341
Native CDs					
SDS + β-CD[d]	0.9997	0.9994	1.11×10^{-6}	5	380–400
SDS + γ-CD[e]	0.9997	0.9993	1.27×10^{-6}	5	312–365
Modified CDs					
SDS + Me-β-CD[f]	0.9998	0.9996	8.20×10^{-7}	5	326–365
SDS + HP-β-CD[g]	0.9973	0.9946	9.99×10^{-6}	5	316–366
Mixed CDs with SDS					
SDS + γ-CD + Me-β-CD[h]	0.9155	0.8382	3.08×10^{-4}	5	320–330
SDS + γ-CD + HP-β-CD[i]	0.9915	0.9831	3.15×10^{-5}	5	325–366
SDS + Me-β-CD + HP-β-CD[j]	0.9966	0.9932	1.28×10^{-5}	5	320–339

[a] 7.5 mM γ-CD, 7.5 mM Me-β-CD, and 3.75 mM TME.
[b] 7.5 mM γ-CD, 7.5 mM HP-β-CD, and 3.75 mM TME.
[c] 7.5 mM Me-β-CD, 7.5 mM HP-β-CD and 3.75 mM TME.
[d] 7.5 mM SDS, 7.5 mM β-CD, and 3.75 mM TME.
[e] 7.5 mM SDS, 7.5 mM γ-CD, and 3.75 mM TME.
[f] 7.5 mM SDS, 7.5 mM Me-β-CD, and 3.75 mM TME.
[g] 7.5 mM SDS, 7.5 mM HP-β-CD, and 3.75 mM TME.
[h] 7.5 mM SDS, 7.5 mM γ-CD, 7.5 mM Me-β-CD, and 3.75 mM TME.
[i] 7.5 mM SDS, 7.5 mM γ-CD, 7.5 mM HP-β-CD, and 3.75 mM TME.
[j] 7.5 mM SDS, 7.5 mM Me-β-CD, 7.5 mM HP-β-CD, and 3.75 mM TME.

Table 4
Relative errors obtained for D-tryptophan methyl ester hydrochloride using individual cyclodextrin host molecules in combination with sodium dodecyl sulfate surfactant

Actual mol fraction	SDS + β-CD		SDS + γ-CD		SDS + Me-β-CD		SDS + HP-β-CD	
	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.
0.328	0.443	35.1	0.304	−7.3	0.397	21	0.350	6.7
0.452	0.272	−40	0.524	16	0.551	22	0.447	−1
0.548	0.760	38.7	0.569	3.8	0.529	−3.5	0.577	5.3
0.620	0.627	1	0.647	4.4	0.578	−6.8	0.595	−4.0
0.715	0.717	0.3	0.632	−12	0.625	−13	0.744	4.1
0.752	0.495	−34.2	0.863	14.8	0.682	−9	0.791	5.2
0.844	0.678	−19.7	0.886	5.0	0.816	−3.3	0.934	11
0.892	0.655	−26.6	1.130	26.7	0.773	−13.3	0.919	3.0
RMS %R.E.		28.7		13.4		13.3		5.7

Table 5
Relative errors obtained for D-tryptophan methyl ester hydrochloride using mixed cyclodextrin host molecules

Actual mol fraction	γ-CD + Me-β-CD		γ-CD + HP-β-CD		Me-β-CD + HP-β-CD	
	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.
0.328	0.370	13	0.135	−58.8	0.266	−19
0.452	0.530	17	0.415	−8.2	0.495	9.5
0.548	0.607	11	0.568	4	0.437	−20.3
0.620	0.636	2.6	0.675	8.9	0.737	18.9
0.715	0.831	16.2	0.866	21.1	0.800	12
0.752	0.884	17.6	0.841	12	0.666	−11
0.844	0.914	8	1.210	43.4	0.992	17.5
0.892	0.974	9.2	1.250	40.1	0.985	10
RMS %R.E.		12.8		31.0		15.4

previous study with those obtained in this study with TME, the presence of the surfactant might provide some small beneficial effect.

3.2.2. *Studies with mixed cyclodextrins in the absence of surfactant*

This and previous studies [17–20] have all shown that the predictive ability of regression models made with various chiral analytes and various CDs are highly dependent on the chiral analyte and the CD used. At this time, not enough is known to reliably predict a priori which CD will give the best results with a given chiral analyte. As a result, it was hypothesized that a mixture of CDs might allow a given chiral analyte to choose an optimum CD with which to bind. Table 5 shows the results obtained for the validation studies with TME and various mixed CDs in the absence of surfactant. Compared with the results obtained with single CDs in this and previous studies (∼5% or less for most studies with the optimum CD), the use of mixed CDs did not seem to offer any improvement in predictive ability. Indeed, when a mixture of Me-β-CD and HP-β-CD was used, the RMS %R.E. value increased to 15.4% compared with 5.7% when HP-β-CD was used alone.

Table 6
Relative errors obtained for D-tryptophan methyl ester hydrochloride using mixed cyclodextrin host molecules in combination with sodium dodecyl sulfate surfactant

Actual mol fraction	SDS + γ-CD + Me-β-CD		SDS + γ-CD + HP-β-CD		SDS + Me-β-CD + HP-β-CD	
	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.	Predicted mol fraction	%R.E.
0.328	0.515	57	0.464	41.5	0.255	−22
0.452	0.484	7.1	0.467	3.3	0.573	26.8
0.548	0.534	−2.6	0.631	15	0.665	21.4
0.620	0.613	−1	0.739	19.2	0.692	12
0.715	0.757	5.9	0.755	6	0.759	6.2
0.752	0.764	1.6	0.798	6.1	0.873	16.1
0.844	0.982	16.4	0.992	17.5	0.992	17.5
0.892	1.070	20.0	1.040	16.6	1.030	15.5
RMS %R.E.		22.4		19.3		18.2

3.2.3. Studies with mixed cyclodextrins in the presence of surfactant

Finally, Table 6 shows the results of the validation studies done with TME with mixed CDs in the presence of SDS surfactant. As with mixed CDs in the absence of surfactant, the use of mixed CDs in the presence of surfactant seems to offer no improvement in predictive ability and may actually reduce the predictive ability over that observed with mixed CDs alone.

4. Conclusions

All the factors that influence chiral analysis by regression modeling of spectral data are not completely clear at this time, and more studies are needed to have a better understanding of the role that CD guest–host inclusion complexation plays in this application. In this study, we investigated the use of an achiral surfactant (SDS) as a powerful solubilizing additive for large hydrophobic molecules. However, the factors that increase the solubility of a chiral analyte may not necessarily improve inclusion complex formation with the cyclodextrin chiral auxiliary. For example, the presence of SDS may result in differential partitioning of guest molecules between SDS micelles and the CD cavity, which may ultimately result in poor CD guest–host inclusion complex formation. In this study, we found that the presence of SDS in most cases either had little effect on the predictive ability of the model or it actually reduced the predictive ability of the model. Moreover, we found that the use of mixed CDs, either in the presence or absence of SDS, reduced the predictive ability of the regression model when compared with results obtained with individual CDs.

Acknowledgment

We thank CAMO Inc. for the donation of chemometric software.

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