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Comparison of the factors that contribute to retention on immobilized polysaccharide-based chiral stationary phases and macrocyclic glycopeptide chiral stationary phases with the Abraham model☆

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ABSTRACT

The Abraham model of linear solvation energy relationship (LSER) was utilized to characterize three recently commercialized chiral stationary phases (CSPs), the Chiralpak IA, IB and IC. Normal phase system constants were determined by HPLC for these three CSPs and compared to literature values for the Chirobiotic T and V CSPs. The results indicate that the Chirobiotic T and V CSPs participate in more polar interactions, such as hydrogen bonding and dipolar interactions, than the three immobilized derivatized polysaccharide CSPs. Additionally, differences were noted for the *e* and *b* terms of the Abraham model (polarizable interactions and hydrogen bond acidity) for the IA and IB CSPs, which are nominally similar CSPs in their chemical makeup.

1. Introduction

The importance of chiral separations to the pharmaceutical industry cannot be understated [1]. Given the ability of biological systems to interact with and metabolize enantiomers differently, the determination of enantiomeric excess continues to be an important aspect of drug development. Increasingly, new active pharmaceutical ingredients are developed as single enantiomer drug substances. Growth in the pharmaceutical industry will continue to drive the need for chiral separation methods. A variety of broadly applicable chiral selectors and chiral stationary phases (CSPs) are necessary to meet the expected need for enantiomeric separations of diverse compounds.

The most applicable chiral stationary phases are based on the linear derivatized polysaccharide family and the macrocyclic glycopeptide family of chiral selectors. These chiral selectors have been commercialized as the Chiralpak, Chiralcel, and Chirobiotic CSPs. One testimony to the applicability of these two classes of chiral selectors is the recent trend in publications on chiral separation screening methods in which these CSPs are highly utilized [2–12]. The most recent improvement in the linear derivatized polysaccharide family of chiral selectors is the immobilization of the polysaccharide onto silica [13–16]. This innovation provides many advantages including: improved ruggedness, few to no solvent restrictions, and modified enantioselectivity (compared to the coated CSPs) [17]. An important aspect of method development on new CSPs is understanding and optimizing the factors that lead to chromatographic retention and selectivity on a particular CSP.

The linear solvation energy relationship (LSER) developed by Abraham has been used for years to understand the intermolecular processes controlling retention in liquid chromatography [18]. In more recent years, it has been applied to study chiral stationary phases [19–25]. The relationship

$$\log k = c + eE + sS + aA + bB + vV \quad (1)$$

equates the logarithm of the retention factor to the interactions the solute experiences between the stationary and mobile phases [26]. The variables *E*, *S*, *A*, *B*, and *V* are solute descriptors whose definitions are as follows. *E* is an excess molar refraction that is obtained from a compound's measured refractive index. *S* is the solute dipolarity/polarizability. *A* and *B* are the hydrogen bond acidity and basicity of a solute, respectively, and *V* is the McGowan volume (in $cm^3/100$). The corresponding terms, *c*, *e*, *s*, *a*, *b*, and *v*, are system constants obtained by multiple linear regression analysis and are defined as follows. The *e* term is the system's ability to interact through polarizable *n* and π electrons. The *s* term is the system's

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ability to interact via dipolar interactions. The *a* and *b* terms are the system's hydrogen bond basicity and acidity, respectively (an acidic solute will interact with a basic phase). The *v* term represents dispersion interactions and the cavity formation energy between the mobile phase and the stationary phase. The *c* term contains the chromatographic phase ratio.

The utility of this LSER for understanding chromatographic retention is apparent, however the application of Eq. (1) to understanding chiral separations is less obvious. Recently, Berthod et al. [24,25] have studied enantioselectivity by Abraham's LSER that has been restated in terms of selectivity.

$$\log \alpha = e\Delta E + s\Delta S + a\Delta A + b\Delta B + v\Delta V \quad (2)$$

Eq. (2) suggests that chromatographic selectivity between two solutes is due to the difference in the solute descriptors for each type of interaction encoded by Eq. (1). The first step in using this relationship to study selectivity is to generate an array of system constants for a particular stationary phase/mobile phase. The array of system constants can then be regressed to obtain the solute descriptors for solutes. The terms of Eq. (2) can then be computed to reveal the importance of a particular intermolecular interaction to selectivity. To perform this type of study on chiral separations, it is necessary to obtain an array of system constants for a CSP and retention factors for a given pair of enantiomers. The system constants are obtained by regression analysis of the retention factors and solute descriptors for achiral solutes. It is necessary to use achiral solutes so as not to create any confusion or bias in the system constants; in other words, if a chiral solute was used and the enantiomers were separated by the CSP, it would be unclear which retention factor should be used as part of the regression analysis. Solute descriptors are then obtained for each enantiomer. The differences in the solute descriptors are indicative of the differences in intermolecular interactions that lead to the enantiomeric separation. It is important to note that this approach assumes that each enantiomer associates with the chiral selector domain differently and forms different transient diastereomeric complexes that allow for the separation of enantiomers [25].

Dolan and co-workers have recently developed a different method for the study of selectivity. The hydrophobic subtraction model (HSM) is specialized to the retention parameters active in the reversed-phase mode [27–30]. Ethylbenzene is used as a reference compound, and the model

$$\log k - \log k_{\text{ethylbz}} = \log \alpha = \eta' H - \sigma' S + \beta' A + \alpha' B + \chi' C \quad (3)$$

describes reversed-phase selectivity in five terms, hydrophobicity ($\eta' H$), steric hindrance ($\sigma' S$), hydrogen bonding with the chromatographic phase acting as a H-bond donor ($\beta' A$) and acceptor ($\alpha' B$), and cation exchange ($\chi' C$). This HSM has proven very useful at characterizing stationary phase selectivity [31]. Despite the success of this approach, the Abraham model LSER is more suitable for the characterization of chiral stationary phases. This is primarily due to the HSM's specialization to the reversed-phase mode. Additionally, some intermolecular interactions are not accounted for in Eq. (3), such as anion exchange (which the macrocyclic glycopeptides based CSPs are capable of [32,33]), dipolar interactions, and π–electron complexation. It should be noted that Dolan and co-workers have demonstrated that these last two interactions may be incorporated into Eq. (3) [34–36].

The aim of this research is to compare the intermolecular forces that contribute to retention on two classes of CSPs: macrocyclic glycopeptides and immobilized derivatized polysaccharides. The basis of comparison will be the LSER system constants obtained for each CSP. Given the importance of the normal phase mode to chiral separations and the efficacy of these particular CSPs in the normal phase mode, the system constants will be obtained for each CSP in the normal phase mode at identical mobile phase compositions.

2. Experimental

2.1. Reagents

Ethanol was purchased from AAPER alcohol (Shelbyville, KY). HPLC grade heptane was purchased from EM Sciences (Gibbstown, NJ). The Chiralpak CSPs were purchased from Chiral Technologies (West Chester, PA). Table 1 describes the CSPs studied. LSER probe molecules were purchased from Aldrich (St. Louis, MO) in high purity grade. The probe solutes are listed in Table 2 with their solute descriptors, which were obtained from Refs. [26,37].

2.2. Equipment and conditions

The HPLC system consisted of a 1200 series binary pump, autosampler, column thermostat, and diode array UV detector (Agilent, Palo Alto, CA). Detection was by UV at 210 nm. Chromatographic data was acquired from a Thermo A2D with Thermo Atlas chromatographic data system (v8.2, Thermo Electron, USA). All chromatographic measurements were made at 25 °C with an eluent flow rate of 1.0 mL/min. The mobile phase, 10/90 ethanol/heptane, was formed by mixing pure ethanol and heptane with a high pressure binary pump.

2.3. Calculations

Retention factors (k) were calculated using the equation $k = (t_r - t_M)/t_M$. The dead time (t_M) was measured from the retention of 1,3,5-tri-*tert*-butylbenzene. Multiple linear regression analysis and statistical calculations were performed using JMP statistical analysis software (vendor SAS).

3. Results and discussion

3.1. Chiral stationary phases

The chiral selectors studied here are illustrated in Fig. 1, and the properties of the CSPs are listed in Table 1. The Chirobiotic T and Chirobiotic V utilize the macrocyclic glycopeptides teicoplanin and vancomycin as chiral selectors. These macrocyclic glycopeptides have been well described previously [32]. Briefly, they are

Table 1
Characteristics of the CSPs used

Column code	Trade name	Description	Dimension
T	Chirobiotic T	Teicoplanin covalently bound to silica gel	50 mm × 4.6 mm, 5 μm
V	Chirobiotic V	Vancomycin covalently bound to silica gel	50 mm × 4.6 mm, 5 μm
IA	Chiralpak IA	Amylose derivatized with tris(3,5-dimethylphenylcarbamate), immobilized onto silica gel	250 mm × 4.6 mm, 5 μm
IB	Chiralpak IB	Cellulose derivatized with tris(3,5-dimethylphenylcarbamate), immobilized onto silica gel	250 mm × 4.6 mm, 5 μm
IC	Chiralpak IC	Cellulose derivatized with tris(3,5-dichlorophenylcarbamate), immobilized onto silica gel	250 mm × 4.6 mm, 5 μm

The system constants for the *T* and *V* are obtained from the literature from Refs. [24,25].

Table 2
Probe solutes and their solute descriptors

Probe solute	*E*	*S*	*A*	*B*	*V*	log *k*
Nitromethane	0.3130	0.95	0.06	0.31	0.4240	0.05
DMF	0.3670	1.31	0.00	0.74	0.6468	0.54
Pyridine	0.7940	0.87	0.00	0.62	0.6753	0.12
Uracil	0.8100	1.00	0.44	1.00	0.7516	0.88
Phenol	0.8050	0.89	0.60	0.31	0.7751	−0.08
DMA	0.3630	1.33	0.00	0.78	0.7877	0.48
1,3-Benzenediol resorscinol	0.9800	1.00	1.10	0.58	0.8338	0.48
Toluene	0.6010	0.52	0.00	0.14	0.8573	−0.69
Benzonitrile	0.7420	1.11	0.00	0.33	0.8711	−0.12
1,3,5 Trihydroxy benzene	1.3550	1.12	1.40	0.82	0.8925	0.99
4-Chlorophenol	0.9150	1.08	0.67	0.20	0.8970	−0.09
o-Cresol	0.8400	0.86	0.52	0.30	0.9160	0.02
3-Cyanophenol	0.9300	1.55	0.77	0.28	0.9300	0.00
4-Nitrophenol	1.0700	1.72	0.82	0.26	0.9490	0.11
4-Bromophenol	1.0800	1.17	0.67	0.20	0.9501	−0.05
Benazamide	0.9900	1.50	0.49	0.67	0.9728	0.47
Ethyl benzene	0.6130	0.51	0.00	0.15	0.9980	−0.67
P-Xylene	0.6130	0.52	0.00	0.16	0.9982	−0.80
4-Iodophenol	1.3800	1.22	0.68	0.20	1.0333	0.02
Phenylurea	1.1000	1.33	0.79	0.79	1.0726	0.60
Naphthalene	1.3400	0.92	0.00	0.20	1.0854	−0.49
Acetanilide	0.8700	1.40	0.50	0.67	1.1133	0.19
Methyl 4-hydroxybenzoate	0.9000	1.37	0.69	0.45	1.1313	0.14
Propyl benzene, *n*-	0.6040	0.50	0.00	0.15	1.1391	−0.77
1-Napthol	1.5200	1.05	0.61	0.37	1.1441	0.03
3-Phenyl-1-propanol	0.8210	0.90	0.30	0.67	1.1978	−0.03
n-Ethyl 4-hydroxybenzoate	0.8600	1.35	0.69	0.45	1.2722	0.02
Butyl benzene	0.6000	0.51	0.00	0.15	1.2800	−0.85
Biphenyl	1.3600	0.99	0.00	0.22	1.3242	−0.42
Caffeine	1.5000	1.60	0.00	1.33	1.3632	1.14
Dibenzo thiophene	1.9590	1.31	0.00	0.20	1.3791	−0.27
n-Propyl 4-hydroxybenzoate	0.8600	1.35	0.69	0.45	1.4131	−0.04
Anthracene	2.2900	1.34	0.00	0.26	1.4544	−0.28
Benzophenone	1.4470	1.50	0.00	0.50	1.4808	−0.22
n-butyl 4-hydroxybenzoate	0.8600	1.35	0.69	0.45	1.5540	−0.07
hexanophenone	0.7200	0.95	0.00	0.50	1.5780	−0.44
Pyrene	2.8080	1.71	0.00	0.28	1.5846	−0.29
Heptanophenone	0.7200	0.95	0.00	0.50	1.7180	−0.45
Minimum value	0.3130	0.5000	0.0000	0.1400	0.4240	−0.8451
Maximum value	2.8080	1.7200	1.4000	1.3300	1.7180	1.1449
Range	2.4950	1.2200	1.4000	1.1900	1.2940	1.9900

The log *k* data is obtained for the IB CSP in the normal phase mode with a mobile phase of 10/90 heptane/ethanol.

composed of a seven residue polypeptide that is crosslinked by various phenolic groups. Both of these chiral selectors are glycosylated to varying degrees, and the teicoplanin selector has a 9-unit alkyl chain (although there are several homologs in this chain length). Both of these selectors possess one ionizable carboxylic acid group and amine groups (1 for teicoplanin, 2 for vancomycin).

The Chiralpak IA utilizes tris-3,5-dimethylphenylcarbamate of amylose immobilized onto silica and is analogous to the coated Chiralpak AD CSP. The Chiralpak IB is tris-3,5-dimethylphenylcarbamate of cellulose immobilized onto silica and is analogous to the coated Chiralpak OD CSP. The Chiralpak IC is tris-3,5-dichlorophenylcarbamate of cellulose immobilized onto silica. This chiral selector has never been commercialized previously as a coated CSP, as it is too soluble in common solvents [17].

3.2. Test compounds

The CSPs were interrogated with 38 probe solutes (see Table 2). This probe set contained ketones, aldehydes, amides, halogenated phenols, alkyl benzenes, polyaromatic hydrocarbons, nitro-substituted benzenes and nitro alkanes. The solute descriptors of these compounds span a wide range. Care was taken to select solutes such that solute descriptor intercorrelation was minimized (Table 3). The low correlation coefficients demonstrate that the solute descriptors are independent of each other (which is necessary for regression analysis).

3.3. System constants for the five CSPs in the normal phase mode

Table 4 and Fig. 2 present the system constants obtained for each CSP in the normal phase mode with a mobile phase composition of 10% ethanol in heptane. The system constants for the Chirobiotic T and Chirobiotic V were obtained from the literature [24]. Generally, the quality of the regression analysis (R^2, *F*, S.E. of regression) was typical of other studies performed in the normal phase mode [24,25,38–41]. Additionally, the quality of regression analysis for the IA CSP was noticeably worse than for the other CSPs. This may indicate that one or more of the probe solutes are interacting with the system in a manner inconsistent with the other test solutes. Following the recommendations of Vitha and Carr [18], residual analysis was performed as part of the regression analysis. The plot of predicted vs. measured log *k* values (Fig. 3) contains no individual solutes with unduly large difference in the predicted vs. measured log *k*. The source of this poor fit for the IA CSP is unclear. The "leave one out" cross validation method was used to assess the generality of the regressions and no strongly influencing solutes were detected. Additionally, the root mean square error of each regression was small in magnitude, 0.1, compared to the system constants.

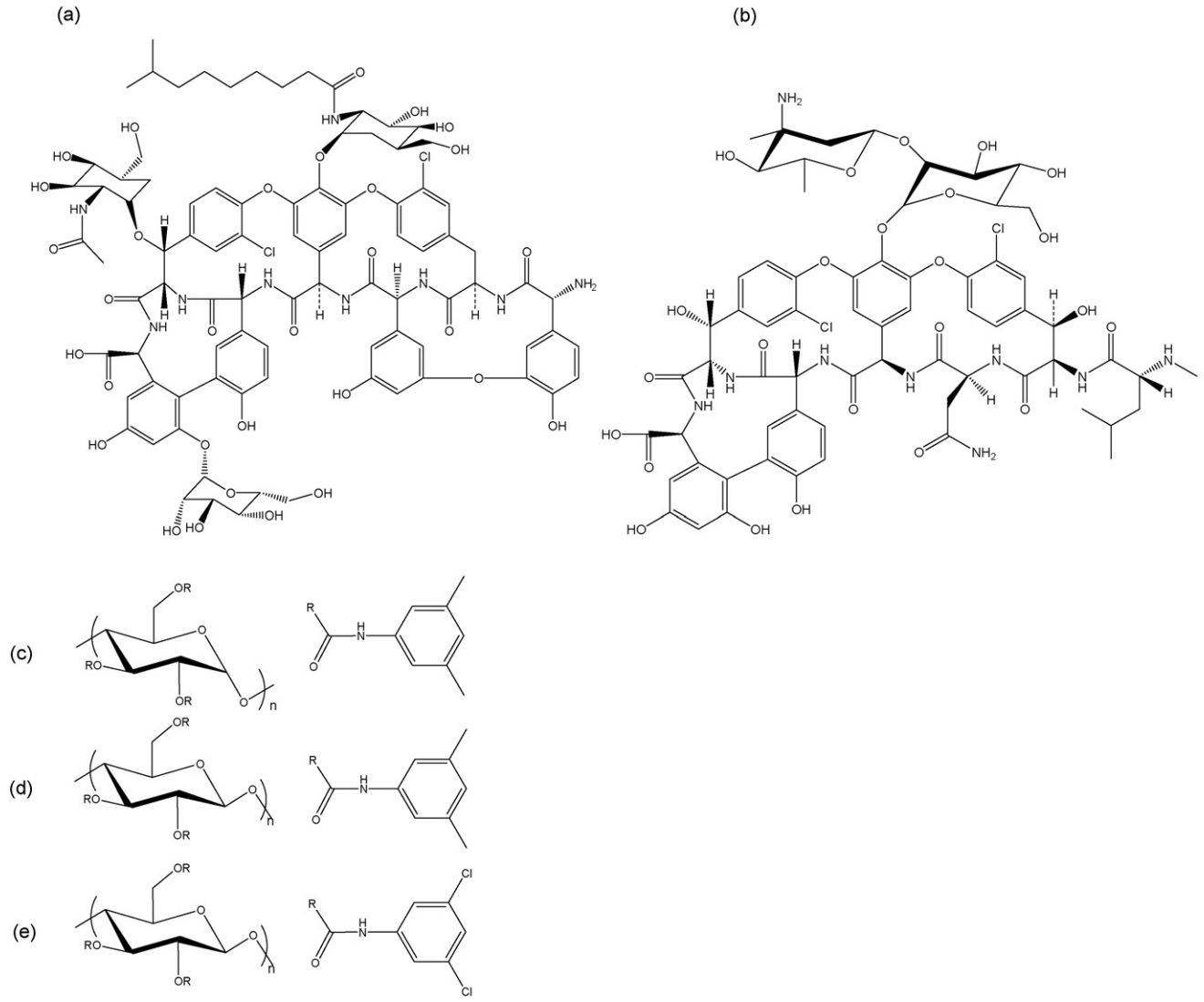

Fig. 1. (a) Chemical structure of teicoplanin, (b) chemical structure of vancomycin, (c) structural components of IA CSP, (d) structural components of IB CSP, (e) structural components of IC CSP.

Table 3
Correlation matrix for probe solutes used in this study

	E	*S*	*A*	*B*	*V*
E	1.00				
S	0.48	1.00			
A	0.01	0.30	1.00		
B	−0.06	0.38	0.16	1.00	
V	0.50	0.23	−0.20	−0.06	1.00

Values are correlation coefficients (*R*).

Fig. 4 presents the normalized system constants for each CSP in bars of equal length. Examination of the size of the segment for each system constant allows for easy comparison of the relative importance of each interaction to retention. Generally, the most important interaction that leads to an increase in retention is hydrogen bond donation by the stationary phase (*b* term), and the most important interactions that lead to a decrease in retention are dispersion interactions and the cavity formation process in the mobile phase (interactions encoded by the *v* term).

Table 4
The system constants obtained for each CSP in the normal phase mode with a mobile phase of 10/90 ethanol/heptane

Column Code	*e*	*s*	*a*	*b*	*v*	Intercept	R^2	S.E.	*F*	*n*
T	0	0.664 (0.06)	0.542 (0.04)	1.796 (0.07)	−0.979 (0.06)	−0.510 (0.07)	0.98	0.112	506	46
V	0	0.871 (0.06)	0.607 (0.04)	1.578 (0.07)	−0.914 (0.04)	−0.611 (0.06)	0.99	0.085	789	39
IA	0	0.438 (0.06)	0.273 (0.05)	0.965 (0.1)	−0.395 (0.07)	−0.628 (0.09)	0.92	0.111	99	38
IB	0.157 (0.04)	0.285 (0.06)	0.313 (0.04)	1.265 (0.06)	−0.591 (0.06)	−0.519 (0.07)	0.97	0.089	207	38
IC	0	0.304 (0.06)	−0.121 (0.05)	1.726 (0.06)	−0.490 (0.06)	−0.583 (0.06)	0.97	0.093	287	38

The values in parentheses are the standard error of each system constant.

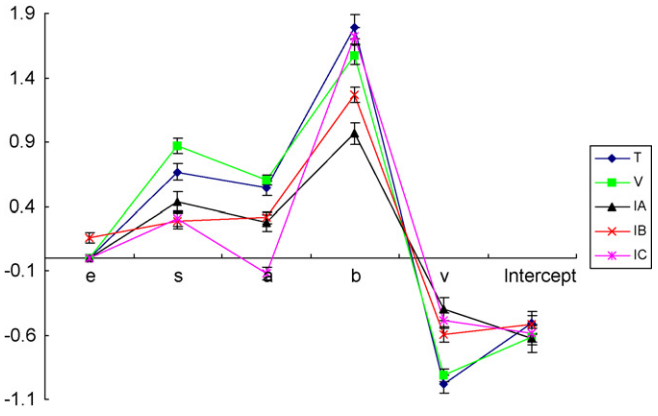

Fig. 2. System constants with error bars for the five CSPs in the NPLC mode with 10/90 ethanol/heptane mobile phase.

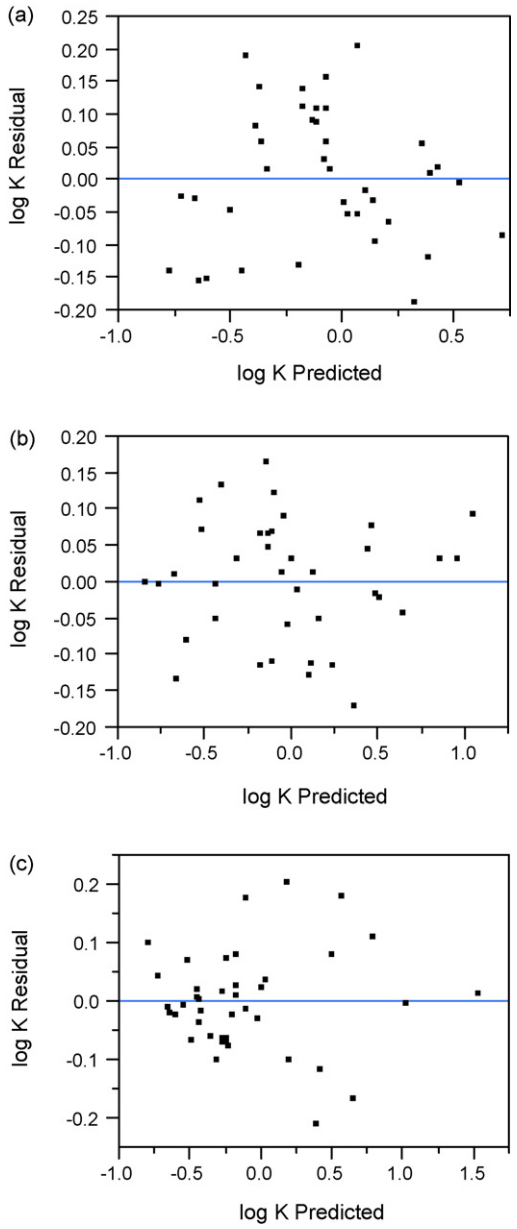

Fig. 3. Plot of residual vs. predicted log *k* for the (a) IA CSP, (b) IB CSP, (c) IC CSP.

3.3.1. *c* term

The *c* term is a system constant that is unique to each chromatographic system. It contains the chromatographic phase ratio. It is the intercept of regression analysis and is not related to any solute property. From Table 4, the *c* terms are indistinguishable from each other for all the CSPs examined here. Values for the *c* term span the range from −0.63 to −0.52 for the immobilized derivatized polysaccharides CSPs and from −0.61 to −0.51 for the macrocyclic glycopeptides. As the *c* term contains no information on solute-stationary phase interaction, no further discussion will be made regarding it.

3.3.2. *v* term

The *v* term encodes dispersion interactions and the cavity formation energy between the mobile phase and the stationary phase. For the five CSPs examined here, the *v* terms are all negative, which is consistent with other normal phase mode LSER studies [24,25,38–41]. The negative *v* term indicates that the cavity formation step of the solvation process occurs more easily in the mobile phase than it does in the stationary phase. Heptane, the bulk component of the mobile phase, is not a cohesive liquid. Consequently, the cavity formation process occurs readily. Additionally, the negative *v* term indicates that the mobile phase participates in dispersion interactions with the solute to a greater extent than the stationary phase. The *v* term for the two macrocyclic glycopeptide CSPs is more negative than the *v* term for the immobilized derivatized polysaccharides CSPs, which suggests that more dispersion interactions are occurring in the derivatized polysaccharides CSPs than in the macrocyclic glycopeptide CSPs. This is an indication that the derivatized polysaccharides CSPs have more non-polar character than the macrocyclic glycopeptide CSPs.

3.3.3. *a b and s terms*

The *a* and *b* terms describe the system's ability to donate and accept a lone pair of electrons in a hydrogen bond, respectively. All five of the CSPs studied here have positive *b* terms, indicating the presence of acidic hydrogen's capable of accepting lone electrons in a hydrogen bond. The positive sign of the *b* term indicates that the stationary phase participates in hydrogen bonding acceptance to a greater extent than the mobile phase. The T and IC CSPs have the greatest *b* terms, followed by the *V* CSP. The IB and IA CSPs have the lowest measured *b* term. Both vancomycin and teicoplanin, the chiral selectors for the *V* and *T*, have many groups that possess acidic hydrogen's (hydroxyls, amines, carboxylic acids,

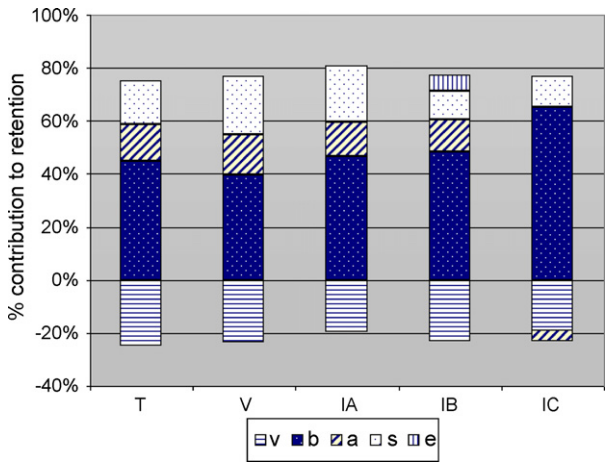

Fig. 4. Stacked bars with each segment representing the normalized system constants contribution to retention. See Table 1 for CSP designations.

the peptide bonds). The derivatized polysaccharides also possess an acidic hydrogen atom in the carbamate linkage of the derivatization group. The data indicates that the macrocyclic glycopeptides participate in hydrogen bond acceptance. Additionally, there is significant variation in the hydrogen-bonding acceptance of the three immobilized derivatized polysaccharide CSPs; therefore, the derivatized polysaccharides participate in hydrogen bonding to a variable extent. The primary difference between the IA and IB CSPs is the stereochemistry of the $1 \rightarrow 4$ saccharide bond (alpha for amylose/IA, beta for cellulose/IB), which results in a 0.3 unit difference in the *b* term for these two CSPs (presumably there is nominally equal coverage of chiral selector on the silica surface). Despite the apparent similarities between the IA and IB CSPs (based on the known parts of the CSP structure in Fig. 1), these differences could be due to different procedures used to immobilize amylose and cellulose. The IC CSP has the highest *b* term of the three immobilized polysaccharide CSPs. This is likely due to an inductive effect caused by the presence of electronegative chlorine atoms on the 3,5-dichlorophenylcarbamate derivatizing group.

The *a* term models the system's ability to donate a lone pair of electrons in a hydrogen bond. The *a* terms of four of the CSPs are positive, but are smaller in magnitude than the *b* terms. The macrocyclic glycopeptides CSPs have similar *a* terms (0.61 and 0.54 for the *V* and *T* CSPs), both of which are greater than the *a* terms of the immobilized derivatized polysaccharides CSPs. The IA and IB have similar *a* values of 0.27 and 0.31, respectively, while the IC has a negative *a* term of −0.12. These results make sense when considering the structures of the selectors. Both families of chiral selectors have a significant number of groups with nonbonding electrons. The macrocyclic glycopeptides are composed of a large number of peptide bonds, as well as hydroxyl, amine and carboxylic acid groups. The derivatized polysaccharides also have a number of nonbonding electrons in the carbamate linkages between the polysaccharide chain and the substituted phenyl groups. The negative *a* term for the IC CSP is likely due to an inductive effect caused by the 3,5-dichlorophenylcarbamate derivatizing group.

The *s* term encodes interactions arising from dipolar interactions between a solute and the chromatographic phases. All of the *s* terms in Table 4 are positive in value, indicating that dipole–dipole interactions increase retention for these CSPs. This is not surprising considering that the mobile phase is quite poor in dipolar character being composed primarily of heptane. The macrocyclic glycopeptide CSPs have greater *s* terms than the immobilized derivatized polysaccharides CSPs. When comparing the structures of these CSPs (Fig. 1), the macrocyclic glycopeptides have a large number of hydroxyls and polypeptide bonds that can participate in dipole-dipole interactions. While the derivatized polysaccharides do have carbamate groups that can also participate in dipolar interactions, these data indicate that the polar groups of the macrocyclic glycopeptides are more able to interact with solutes in this fashion.

When discussing the source of these polar interactions, it is also important to consider the silica support as well as presence of solvent molecules in the stationary phase matrix. Ultimately, the system constants are a measure of the relative difference in interaction between all the components of the stationary phase and the mobile phase.

3.3.4. e term

The *e* term describes intermolecular interactions associated with polarizability of nonbonding *n*- and π-electrons. This includes π-electron stacking and induced dipole interactions (i.e. ion-induced dipole and dipole-induced dipole). The *e* term of four of the CSPs examined is statistically indistinguishable from zero, which is consistent with other normal-phase mode LSER studies [24,25,38–41]. This suggests that the magnitude of the interactions represented by the *e* term are identical in both the mobile phase and stationary phase (thus having zero net impact on retention) or that no polarizable interactions are occurring in this mode of operation with these systems. Interestingly, the IB stationary phase has a measurable *e* term of 0.157. This difference between the IA and IB CSPs is surprising considering that the primary chemical difference between the IA and IB CSPs is the stereochemistry of the $1 \rightarrow 4$ saccharide bond (alpha for amylose/IA, beta for cellulose/IB). Additionally, one might suspect that, all other things being equal, the IC CSP might have more activity through the *e* term as it is derivatized with a dichlorophenyl moiety that is π-electron deficient. In spite of any preconceived notions, the real source of this variation may not be able to be determined as the tertiary structure of the saccharide polymer on the silica support is largely unknown.

4. Conclusions

The system constants for the macrocyclic glycopeptide CSPs and the immobilized derivatized polysaccharide CSPs are typical of the system constants for normal phase stationary phases. The polar interactions, *s*, *a*, and *b* are positive and contribute to retention of a solute. The non-polar interaction, *v*, is negative and reduces the retention of a solute. Polarizable interactions, *e*, are zero for most of these CSPs, which is also similar to other normal phase LSER studies. The data indicates that the macrocyclic glycopeptides are more polar having larger *s*, *a*, and *b* terms, whereas the immobilized derivatized polysaccharide CSPs have more non-polar character; the *v* term for the immobilized derivatized polysaccharide CSPs is less negative than for the macrocyclic glycopeptide CSPs. These results make sense when considering the chemical makeup of the chiral selectors. The macrocyclic glycopeptides have an abundance of polar groups, while the polysaccharides CSPs are derivatized with moieties that are largely non polar, with only the carbamate linkages having some polar character. Additionally, there were several differences observed in the system constants for the IA and IB CSPs, which are nominally very similar. The IB was the only CSP to have a measurable *e* term, while the IA had zero interaction through the *e* term. Additionally, the hydrogen bond acidity of the system, *b*, was also slightly different for these two CSPs, with the IB having a larger hydrogen bond acidity. The system constants obtained for these CSPs can serve as the basis for future studies of enantioselectivity.

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