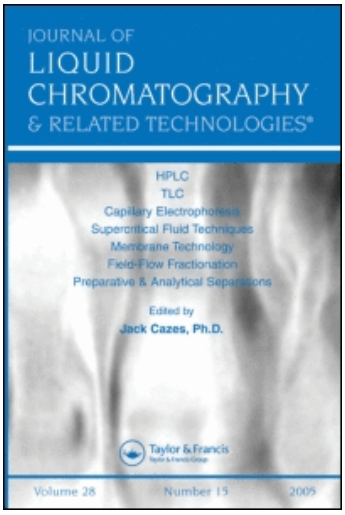

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An Investigation into the Role of Solvation in a Well Characterized Chiral Recognition System

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AN INVESTIGATION INTO THE ROLE OF SOLVATION IN A WELL CHARACTERIZED CHIRAL RECOGNITION SYSTEM

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ABSTRACT

The effect of mobile phase composition upon the thermodynamic parameters of enantiomer adsorption and separation has been studied using a well characterized chiral recognition system. The separation of the enantiomers of a series of *N*-(2-naphthyl) alanine derivatives on an *N*-(3,5-dinitrobenzoyl) leucine-derived chiral stationary phase using various mobile phases was studied at several temperatures. Van't Hoff analysis of the chromatographic data was performed to determine the enthalpy and entropy of enantiomer adsorption and separation. In general, increased enantioselectivities were seen for the less polar mobile phases, although analytes containing polar sites in addition to those required for chiral recognition did show greater enantioselectivities in polar mobile phases capable of solvating these superfluous polar groups.

INTRODUCTION

The role of mobile phase composition in the chromatographic separation of enantiomers on chiral stationary phases (CSPs) has long been empirically

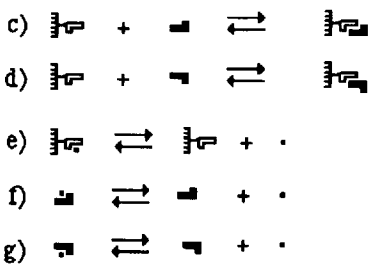
noted, and has recently been the subject of several reports (1-3). As with well studied achiral systems under normal-phase conditions (4), a decrease in retention with increasing mobile phase polarity is generally observed, as is a general decrease in relative retention (*i.e.* enantioselectivity). This indicates that the retentions of the enantiomers are being dissimilarly affected by the mobile phase. We set out to study the origins of this enantioselective solvation behavior by chromatographically separating enantiomers on a given column using a variety of mobile phases and temperatures. Solvation effects were studied using van't Hoff analysis of the chromatographic data to allow comparison of the enthalpy and entropy of adsorption for each enantiomer in different mobile phases.

In a cartoon depiction of the enantiomer separation process, the stationary phase ( ) and analyte enantiomers ( ) are each solvated by (for the sake of simplicity) a single solvent molecule (•). The overall adsorption equilibria for the enantiomers can be represented by a) and b), where a) depicts the formation of the more and b) the less stable diastereomeric adsorbate. In both cases, release of solvent molecules to the bulk mobile phase is represented as occurring upon adsorbate formation.

a) + ⇄ + ••

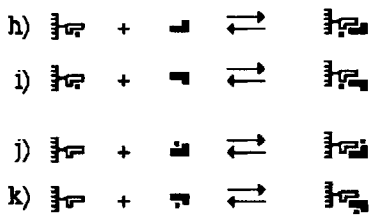
b) + ⇄ + ••

The events depicted above are the summation of the component steps c) through g), where c) and d) represent adsorption of the enantiomers in the absence of solvent, e) represents desolvation of the stationary phase, and f) and g) represent desolvation of analyte enantiomers. The gas phase-like adsorption equilibria, c) and d), will be relatively unaffected by a change in mobile phase and, for the special case of enantiomers in an achiral environment such as the mobile phase, f) and g) must be equivalent. Thus, this simple model predicts that although the absolute retention of the two



enantiomers will be affected by a change in mobile phase, the relative retention, or enantioselectivity, will be unaffected.

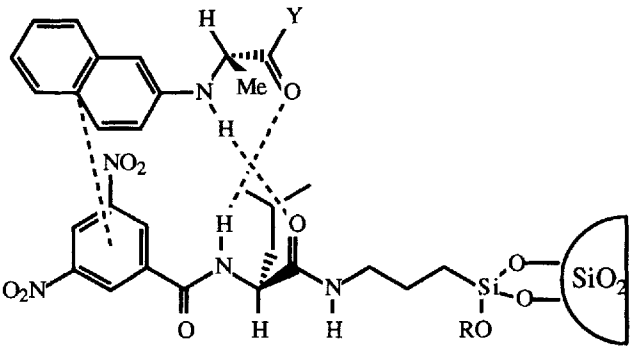
Long time observations of the effect of mobile phase composition on enantioselectivity tell us that the above model must be oversimplified. It is possible that c) and d) are indeed affected differently by mobile phase composition. Since the weak electrostatic interactions responsible for chromatographic retention must be dependent upon the dielectric constant of the medium, and since the number and type of interactions between analyte and CSP can be different for the two enantiomers, a change in the dielectric constant of the chromatographic medium could result in a change in the observed enantioselectivity for a particular separation. Alternatively, the adsorbates shown in h) through m) which are comprised of only partially desolvated stationary phase and/or analyte molecules may also be involved in the retention process. The more retained enantiomer, which undergoes more and stronger associations with the CSP, might require relatively more desolvation upon adsorbate formation, leading to the observed decrease in enantioselectivity with increasing mobile phase polarity.



l) 

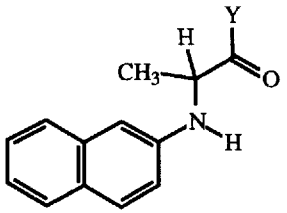
m) 

We chose for this study a CSP derived from *N*-3,5-dinitrobenzoyl leucine (CSP 1), which is widely used and relatively well understood (5,6). We chose as analytes several *N* - (2-naphthyl) amino acid derivatives. The chromatographic separation of analytes of this type with CSP 1 has been reported previously (7). The structure of the more stable complex of selector and analyte, as determined by solution (8) and X-ray studies (9) is shown below in Figure 1. Two hydrogen bonds and one face to face π-π interaction constitute the requisite three simultaneous stereochemically dependent interactions responsible for chiral recognition. The less retained enantiomer, despite a claim to the contrary (10, 11) is conformationally restricted and cannot equally well undergo these three simultaneous interactions. (12)



CSP 1

Figure 1: Chiral recognition mechanism showing retention of an *N* - (2-naphthyl) alanine derivative by CSP 1.
After Pirkle and Pochapsky (8).



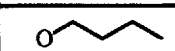
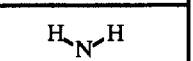
Compound	Y
butyl ester	
diethylamide	
butyl amide	
ammonia amide	

Figure 2: *N*-(2-naphthyl) alanine derivatives used in the study.

In this study, four *N*-(2-naphthyl) alanine derivatives (Figure 2) were synthesized, and their chromatographic behavior upon CSP 1 was studied. The *n*-butyl ester derivative contains as potentially strongly solvated groups only the three sites required for chiral recognition: the π basic naphthyl system, the aniline hydrogen, which functions as a hydrogen bond donor, and the ester carbonyl group, the carbonyl oxygen of which functions as a hydrogen bond acceptor. The diethylamide contains these same interaction sites, although the somewhat larger dipole associated with the amide moeity could lead to additional solvation relative to the ester. The butyl amide and ammonia amide each contain additional hydrogen bond donor sites not required for chiral recognition. These sites are expected to be extensively solvated in mobile phases which are good hydrogen bond acceptors. Differences in retention and enantioselectivity noted between the four analytes in a particular mobile phase are expected to arise principally from differences in Y group solvation and from non-specific adsorption of the analyte by the CSP through polar sites in the Y group.

The mobile phases examined in this study include the hydrogen bond acceptors: tetrahydrofuran, dioxane, acetonitrile, and ethyl acetate; the

hydrogen bond donor/acceptors: methanol and 2-propanol; the hydrogen bond donor chloroform, and the largely dipolar solvent, methylene chloride. In addition, several binary mixtures, including reverse-phase systems, were investigated.

MATERIALS AND METHODS

Apparatus

Chromatographic analysis was performed using a Rainin HPX Rabbit pump, a Rheodyne model 7125 injector with a 20µl sample loop, a Milton Roy LDC UV absorbance monitor D (254 nm), and a Shimadzu CR1A integrating recorder.

Materials

Solvents used were HPLC grade or distilled prior to use. A stainless steel column (4.6 mm ID x 25 cm length) packed with CSP 1 was prepared in-house using a previously reported procedure (7). The four *N*-(2-naphthyl) alanine-derived analytes were prepared by treatment of the corresponding *N*-hydroxysuccinimide-derived active ester with the appropriate alcohol or amine, followed by chromatographic purification. All were satisfactorily characterized by ^{1}H NMR and elemental analysis.

Methods

All chromatographic experiments were carried out at a nominal flow rate of 1.00 ml/min. Variable temperature data were collected with the mobile phase reservoir and pump at ambient temperature, and with the column immersed in a large constant temperature bath. Typically four or five temperatures ranging from 0°C to 90°C were examined. About two feet of 0.009 in ID stainless steel tubing was used to connect the column to the injector and was wrapped around the inverted column as a heat exchanger to thermally equilibrate the mobile phase prior to column entry. Column void volume was determined by measuring the elution time of a 5µL injection of neat dodecane for the normal phase eluents, and the elution time of either deuterium oxide or the neat polar modifier for the reverse phase eluents.

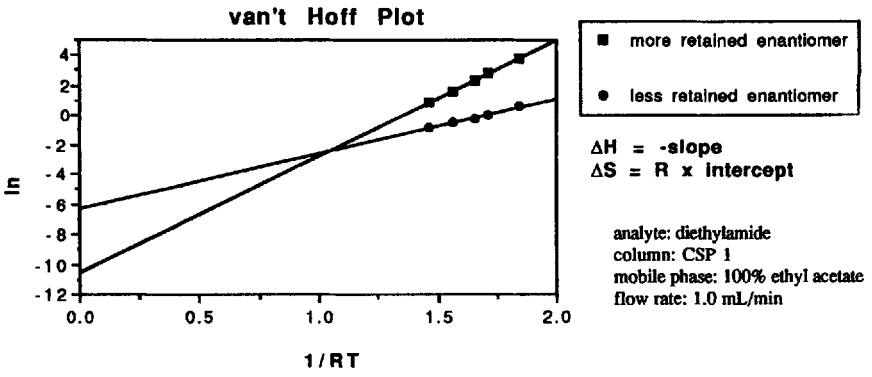


Figure 3: van't Hoff analysis of chromatographic data allows determination of thermodynamic parameters of enantiomer adsorption.

Data reduction was performed using a computer program written for Hypercard™.

RESULTS AND DISCUSSION

Plotting the natural logarithm of capacity factor with respect to inverse absolute temperature allows determination of the thermodynamic parameters of enantiomer adsorption. A typical van't Hoff plot is presented in Figure 3. The points lying on the upper line represent data for the most retained enantiomer, whereas the points lying on the lower line represent data for the least retained enantiomer. The extent of separation between the lines at a given temperature is related to the difference in free energy of adsorption for the two enantiomers at that temperature and determines α, the chromatographic separation factor. Intersection of the lines indicates a temperature at which the enthalpic and entropic contributions to enantioselectivity cancel, and no separation occurs. At temperatures above that at which the lines intersect, an inversion of elution order should occur.

Such inversions, known in gas chromatography (13, 14), have not yet been observed in liquid chromatography so far as we are aware. The enthalpy of adsorption, ΔH_{ads}, is determined from the negative slope of the least squares line through the data points. The entropy of adsorption, ΔS_{ads} is given by the intercept at infinite temperature multiplied by R, the gas constant. Because these van't Hoff plots use capacity factors and not true equilibrium constants, the entropy values obtained differ from the true values by a factor of ln ϕ, where ϕ is the phase ratio. To allow comparison of entropy values, we have made the assumption that phase ratio is independent of mobile phase composition so long as the same column is used. The extrapolation to the intercept at infinite temperature is a long one and the plots are almost certainly non-linear over an extended range of temperature. Nevertheless, the extrapolated values are felt to be pertinent to the retention processes occurring near room temperature.

A summary of the thermodynamic parameters of enantiomer adsorption and separation are presented in Table 1. Using the enthalpy and entropy values obtained from the previously described van't Hoff analysis, capacity factors (k'*) and separation factors (α*) calculated for 25°C are also reported. Solvent polarity (p'), based upon Snyder's modification (15) of the Rohrschneider solvent polarity index, is shown in the first column.

Retention, shown as the natural logarithm of the capacity factor, can be seen in Fig. 4 to generally decrease with increasing mobile phase polarity (p'), although an increase, reflecting the contribution of solvophobic retention, is seen in the water-containing mobile phases. It is tempting to interpret outlying points on the ln k' vs p' graphs as indicative of specific solvation effects not adequately reflected in p'. For example, the abnormally high retention seen for the ammonia amide in methylene chloride could reflect the relative inefficiency of this mobile phase in the solvation of the superfluous amide hydrogens of this analyte. These amide hydrogens are thought to lead to increased non-specific adsorption of the analyte.

Table 1: Chromatographic parameters for the separation of four N-(2-naphthyl) alanine analytes in several mobile phases.
* data calculated for 25°C.

		EtOAc	acetonitrile (AcN)	80% AcN/ water	60% AcN/ water	dioxane	THF	40% THF/ cyclohex	MeOH	80% MeOH/ water	2-propanol (IPA)	80% IPA/ hexane	60% IPA/ hexane	40% IPA/ hexane	20% IPA/ hexane	chloroform	methylene chloride
butyl ester	p'	4.4	5.8	6.7	7.6	4.8	4.0	1.5	5.1	6.1	3.9	3.1	2.4	1.6	0.9	4.1	3.1
	k'1*	0.15	0.13	0.71	3.14	-	-	0.25	0.39	1.72	1.04	0.83	0.88	0.92	1.18	0.17	0.24
	k'2*	0.81	0.51	1.22	5.12	-	-	1.87	1.21	5.05	6.65	5.19	6.92	7.52	10.74	2.08	2.16
	alpha*	5.40	3.92	1.72	1.63	-	-	7.48	3.10	2.94	6.39	6.25	7.86	8.17	9.10	12.24	9.00
	ΔH1	-1.45	-2.11	-3.82	-3.47	-	-	-1.95	-1.99	-4.56	-4.92	-4.58	-5.21	-4.87	-4.03	-1.31	-2.32
	ΔH2	-5.07	-5.43	-5.44	-5.02	-	-	-5.12	-4.65	-7.27	-8.90	-8.47	-9.65	-9.36	-8.51	-5.80	-7.37
	ΔΔH	-3.62	-3.33	-1.61	-1.56	-	-	-3.18	-2.66	-2.71	-3.98	-3.90	-4.44	-4.49	-4.48	-4.49	-5.05
	ΔS1	-8.64	-11.18	-13.50	-9.37	-	-	-9.33	-8.54	-14.22	-16.44	-15.74	-17.73	-16.50	-13.20	-7.96	-10.58
	ΔS2	-17.44	-19.55	-17.86	-13.60	-	-	-15.94	-15.22	-21.18	-26.10	-25.15	-28.54	-27.40	-23.84	-18.01	-23.20
	ΔΔS	-8.80	-8.37	-4.36	-4.23	-	-	-6.61	-6.68	-6.96	-9.86	-9.41	-10.81	-10.90	-10.64	-10.05	-12.62
diethylamide	k'1*	0.97	0.59	0.76	2.22	-	-	1.76	0.55	-	2.52	2.31	2.75	2.89	5.74	1.03	3.86
	k'2*	13.29	5.20	2.88	7.68	-	-	36.13	4.01	-	38.54	31.41	45.81	49.46	104.43	12.34	19.44
	alpha*	13.70	8.81	3.79	3.46	-	-	20.53	7.29	-	15.29	13.60	16.66	17.11	18.19	11.98	5.04
	ΔH1	-3.71	-4.03	-4.03	-3.35	-	-	-3.70	-2.67	-	-6.52	-6.57	-7.60	-6.52	-5.97	-1.13	-3.55
	ΔH2	-7.79	-7.80	-7.11	-6.69	-	-	-7.78	-6.63	-	-11.29	-10.99	-12.34	-11.39	-10.87	-6.11	-7.86
	ΔΔH	-4.08	-3.77	-3.08	-3.34	-	-	-4.08	-3.96	-	-4.77	-4.42	-4.74	-4.87	-4.90	-4.98	-4.31
	ΔS1	-12.51	-14.58	-14.08	-9.66	-	-	-11.29	-10.15	-	-20.04	-20.38	-23.49	-19.77	-16.56	-3.73	-9.23
	ΔS2	-21.00	-22.90	-21.76	-18.40	-	-	-18.98	-19.49	-	-30.63	-30.03	-33.81	-30.47	-27.24	-15.51	-20.48
	ΔΔS	-8.49	-8.32	-7.68	-8.74	-	-	-7.69	-9.34	-	-10.59	-9.65	-10.32	-10.70	-10.68	-11.78	-11.25
butyl amide	k'1*	0.94	0.61	0.87	1.98	0.31	0.19	2.16	0.33	1.10	0.90	0.86	0.90	1.13	2.95	0.98	3.66
	k'2*	4.58	1.72	1.10	2.98	1.54	1.47	16.01	0.80	2.14	5.02	4.31	5.96	7.05	17.54	2.23	6.39
	alpha*	4.87	2.82	1.64	1.51	4.97	7.74	7.41	2.42	1.95	5.58	5.01	6.62	6.24	5.95	2.28	1.75
	ΔH1	-3.24	-3.85	-4.11	-3.18	-1.88	-1.70	-3.26	-2.05	-4.08	-4.60	-4.47	-4.66	-4.45	-3.21	-0.65	-4.13
	ΔH2	-6.45	-6.05	-5.75	-4.55	-5.76	-5.66	-7.03	-4.10	-5.59	-8.20	-7.85	-8.90	-8.24	-7.09	-2.94	-5.67
	ΔΔH	-3.21	-2.20	-1.64	-1.37	-3.88	-3.96	-3.77	-2.05	-1.51	-3.60	-3.38	-4.24	-3.79	-3.88	-2.29	-1.54
	ΔS1	-10.99	-13.89	-14.60	-9.31	-8.62	-9.02	-9.41	-9.09	-13.50	-15.65	-15.29	-15.85	-14.69	-8.62	-2.23	-11.28
	ΔS2	-18.62	-19.22	-19.10	-13.10	-18.47	-18.23	-18.08	-14.21	-17.25	-24.31	-23.44	-26.32	-23.77	-18.10	-8.27	-15.34
	ΔΔS	-7.63	-5.33	-4.50	-3.79	-9.85	-9.21	-8.87	-5.12	-3.75	-8.66	-8.15	-10.47	-9.08	-9.48	-6.04	-4.06
ammonia amide	k'1*	3.65	1.32	0.62	1.30	1.02	0.86	13.32	0.42	0.92	1.79	1.83	3.20	4.05	12.34	9.17	45.80
	k'2*	6.84	2.17	0.84	1.69	1.90	2.06	28.04	0.78	1.52	4.22	3.57	6.06	7.69	21.15	12.08	52.03
	alpha*	1.87	1.64	1.35	1.30	1.86	2.40	2.11	1.86	1.65	2.36	1.95	1.89	1.90	1.71	1.32	1.14
	ΔH1	-3.18	-4.03	-3.84	-3.46	-2.84	-2.46	-3.33	-2.03	-4.26	-4.87	-4.28	-5.94	-5.29	-4.03	-1.47	-5.90
	ΔH2	-4.89	-5.24	-4.85	-4.34	-4.44	-4.47	-5.38	-3.50	-5.51	-6.75	-5.70	-7.28	-6.76	-5.24	-2.45	-6.36
	ΔΔH	-1.71	-1.21	-0.81	-0.88	-1.60	-2.01	-2.05	-1.47	-1.25	-1.88	-1.42	-1.34	-1.47	-1.21	-0.98	-0.46
	ΔS1	-8.10	-12.97	-13.85	-11.09	-9.50	-8.55	-8.03	-8.53	-14.46	-15.19	-13.16	-17.62	-14.97	-8.53	-0.53	-12.20
	ΔS2	-12.59	-16.04	-15.94	-13.52	-13.62	-13.56	-11.43	-12.25	-17.66	-19.79	-16.60	-20.85	-18.63	-11.52	-3.27	-13.49
	ΔΔS	-4.49	-3.07	-2.09	-2.43	-4.12	-5.01	-5.40	-3.72	-3.20	-4.60	-3.44	-3.23	-3.66	-2.99	-2.74	-1.29

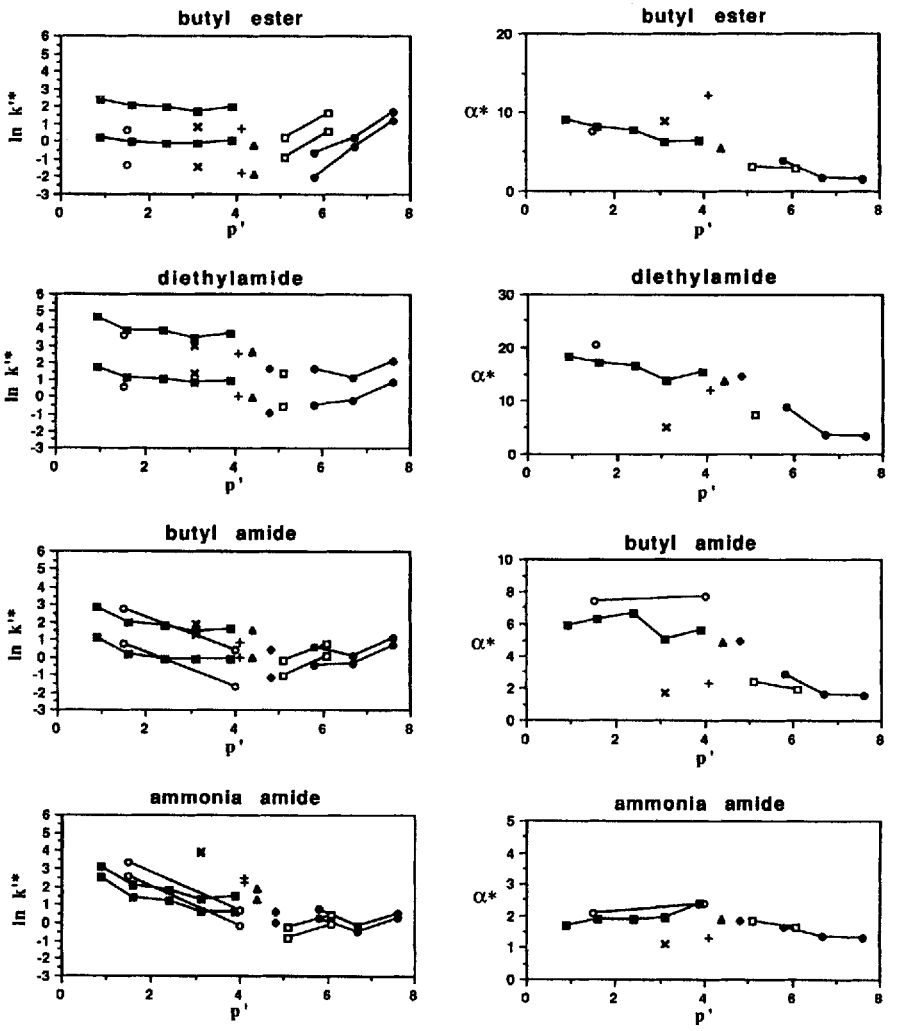


Figure 4: Effect of solvent polarity upon retention and enantioselectivity. ■ IPA / hexane mixtures; ○ THF / cyclohexane mixtures; × methylene chloride; + chloroform; ● ethyl acetate; ◇ dioxane; □ methanol / water mixtures; ● acetonitrile / water mixtures.

The enantioselectivities of the ammonia amide and of the butyl amide appear to be depressed in the less polar mobile phases, resulting in a somewhat bowed curve. This may again arise from the deleterious contribution of nonspecific adsorption to enantioselectivity in the less polar mobile phases. This same reasoning may account for the poor separation of enantiomers of the butyl amide, and especially the ammonia amide, in either methylene chloride or chloroform mobile phases.

Enthalpies and entropies of adsorption obtained from the van't Hoff plots are shown in Figure 5. While the plots are again somewhat non-linear, it is interesting to note that there is a rough parallel between the ΔH and ΔS graphs. That is to say that, in general, highly exothermic adsorption is accompanied by a corresponding large loss in entropy. This is similar to the enthalpy-entropy compensation phenomenon in reverse-phase chromatography described by Horvath and co-workers (16).

Highly exothermic adsorption does not necessarily lead to high enantioselectivity but does tend to worsen band shapes. More important to enantioselectivity is the value of $\Delta\Delta H$, the differential enthalpy of adsorption for the two enantiomers (Figure 6). For the normal phase eluents, the $\Delta\Delta H$ for the butyl ester is most exothermic in methylene chloride and least exothermic in 40% THF/cyclohexane. Presumably THF (and other good hydrogen-bonding solvents) solvate the sites involved in chiral recognition and enthalpically costly desolvation of these sites must take place if chiral recognition is to occur. Similarly, the diethylamide shows the most exothermic $\Delta\Delta H$ in chloroform and the least in ethyl acetate. Interestingly, this trend is reversed for the butyl amide and the ammonia amide, both of which contain additional polar groups not required for chiral recognition. For both of these analytes, THF and ethyl acetate give a more exothermic $\Delta\Delta H$ than methylene chloride or chloroform, presumably because the latter is ineffective in the solvation of analyte polar sites not required for chiral recognition. Thus, in some cases, the beneficial effect of solvation of

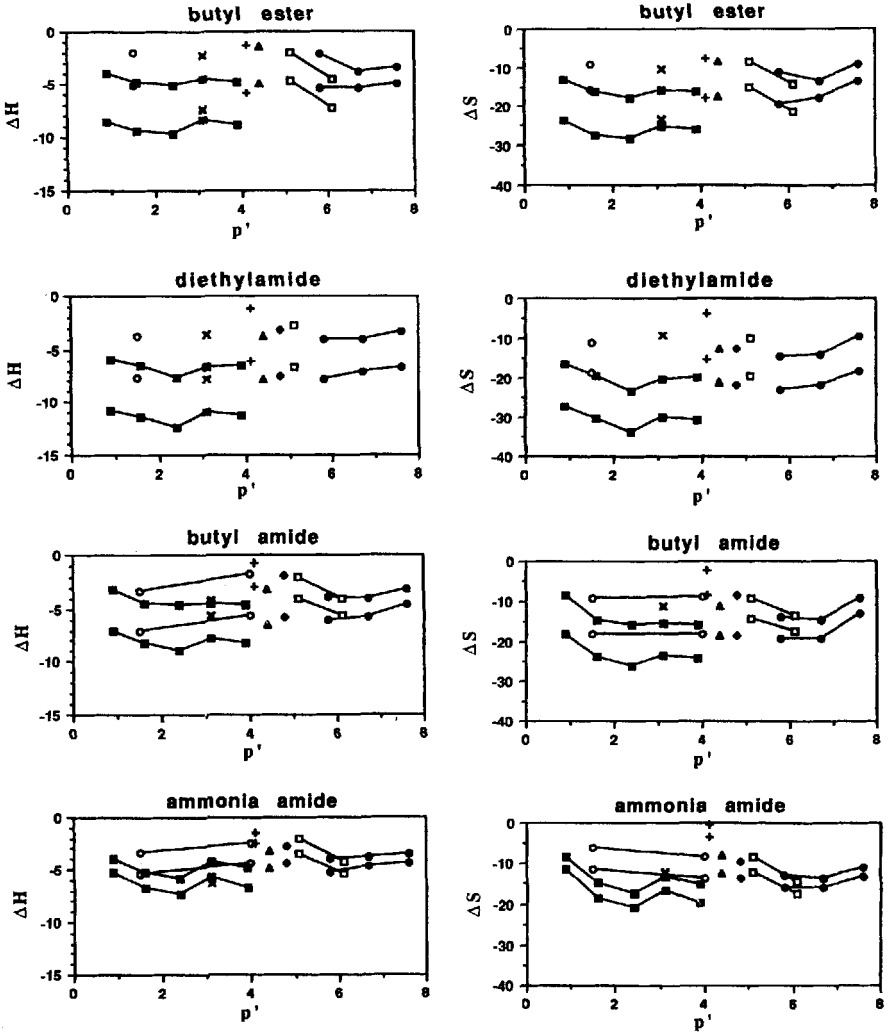


Figure 5: Effect of solvent polarity upon enthalpy and entropy of adsorption. ■ IPA / hexane mixtures; ○ THF / cyclohexane mixtures; × methylene chloride; + chloroform; ▲ ethyl acetate; ◇ dioxane; □ methanol / water mixtures; ● acetonitrile / water mixtures.

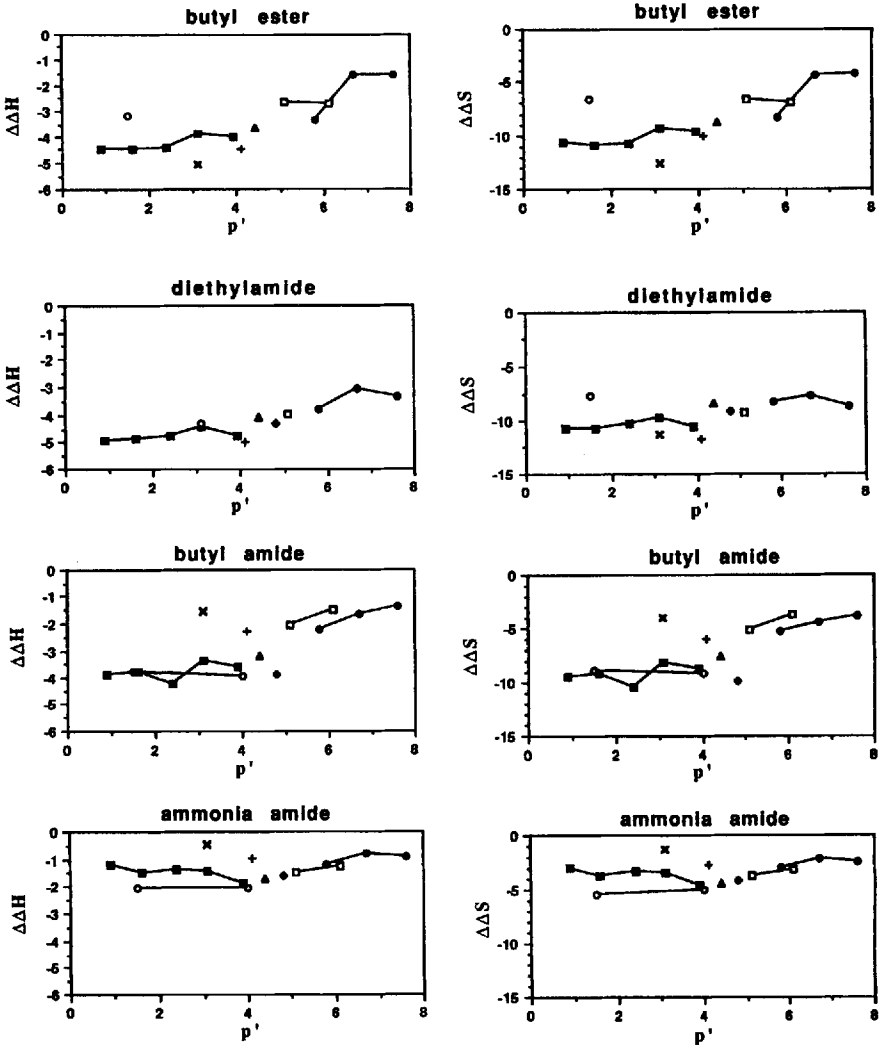


Figure 6: Effect of solvent polarity upon ΔΔH and ΔΔS. ■ IPA / hexane mixtures; ○ THF / cyclohexane mixtures; × methylene chloride; + chloroform; ● ethyl acetate; ◇ dioxane; □ methanol / water mixtures; ● acetonitrile / water mixtures.

extraneous polar sites appears to more than compensate for the deleterious effect of solvation of the polar sites required for chiral recognition.

CONCLUSION

Mobile phase composition has been shown to play an important role in the chromatographic separation of enantiomers. In general, both retention and enantioselectivity are seen to decrease with increasing mobile phase polarity. Thermodynamic studies have revealed that differences in both enthalpy and entropy contribute to the observed dependence of retention and enantioselectivity upon mobile phase polarity. The dependence of enantioselectivity upon mobile phase polarity is thought to result largely from differential solvation of the diastereomeric adsorbates although the present study does not preclude an explanation based solely upon dielectric constant. In general, the greatest enantioselectivity will be seen in less polar mobile phases. However, analytes possessing polar sites in addition to those required for chiral recognition may show the greatest enantioselectivity in more polar mobile phases which solvate these superfluous polar groups.

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