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^{1}H AND ^{13}C NUCLEAR MAGNETIC RESONANCE STUDIES OF ENANTIOSELECTIVE HYDROGEN BONDING OF FLUOROALKYL CARBINOL BY CHIRAL BUTOXYCARBONYL-D-VALINE

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SUMMARY

Studies of the chromatographic selectivity in chiral solute–chiral stationary phase (CSP) systems have been performed with the aid of ^{1}H and ^{13}C nuclear magnetic resonance techniques. For the *R* and *S* enantiomers of 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) in contact with butoxycarbonyl (BOC)-D-valine, the most significant bonding interactions are seen as chemical shifts at the carbonyl carbon and amide proton of the CSP. The differences between the shifts for the two isomers were the same in pure methylene chloride and in hexane–methylene chloride (80:20), suggesting that the solvent does not participate in the chiral recognition mechanism. However, the solvent does participate in the overall retention mechanism as measured by the capacity factor, k', for TFAE that is absorbed by a BOC-D-valine-(spacer)-derivatized silica column packing. Values of the k' decreased with increasing percentage of the strong solvent, methylene chloride.

INTRODUCTION

Pirkle and Sikkenga[1] and others[2–4] have expended considerable effort towards developing chiral derivatization agents for use in high-performance liquid chromatography (HPLC). The newer chiral stationary phases (CSPs) are generally prepared by immobilizing a chiral enantiomer on a silanized porous silica-based material. Pirkle and House[5] have emphasized the importance of a three-point simultaneous interaction to distinguish the handedness of a chiral enantiomer.

Nuclear magnetic resonance (NMR) techniques have been successfully used in the studies of such association interactions. Lochmüller *et al.*[6] reported NMR results of studies of sites of hydrogen-bond formation with two carbonyl-bis-(amino acid esters) and several solutes. Pirkle and Hoover[7] have reported NMR studies of the interaction of chiral fluoroalcohols with a wide variety of solutes.

Our preliminary study was prompted by the pioneering work of Pirkle and Rinaldi[8], in which they showed that the NMR spectra of oxaziridine enantiomers

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were non-identical in the presence of chiral arylperfluoroalkylcarbinols. The resultant chemical shift differences were used for direct determination of the enantiomeric composition of the oxaziridine. The spectral nonequivalences were reasoned to be due to the physical interaction of chiral fluoroalkylcarbinol with enantiomeric solutes to form diastereomeric solutes. Pirkle and Tsipouras[9] have also reported NMR studies of interactions between soluble analogues of 3,5-dinitrobenzoyl (DNB) amino acid esters and the enantiomers of resolvable compounds. It is not essential to the NMR method that diastereomeric solutes have different stabilities. Pirkle also argued that, although a model based upon a sterically defined ease of approach can partially explain the differential chromatographic mobility of diastereomers, it is conceptually bothersome to conclude that solution conformational behavior of conformationally mobile molecules will exert control over chromatographic behavior.

In this paper, we report our attempts to examine the interaction between an enantiomeric solute and a chiral agent, when they are both in solution and also when one is immobilized on silica. The system we have investigated is that of butoxycarbonyl-D-valine (BOC-D-Val) and 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) both of which are shown in Fig. 1. Along with this system, derivatives of other amino acids were also investigated. An attempt has been made to correlate the differences in the chemical shifts, due to these interactions, with the chromatographic separation factor, α, for racemic mixtures.

We also have investigated the chemical and structural nature of the modified surfaces. The study uses conventional solution Fourier transform (FT)-NMR techniqes on suspensions in order to mimic as closely as possible the actual conditions in a liquid chromatographic column. However, cross polarization-magic angle spinning (CP-MAS) studies have beeen used to generate the information about the solid CSPs for identification purposes only.

EXPERIMENTAL

Chemicals and reagents

The amino acid derivatives used were BOC-D-valine (N-*tert.*-butoxycarbonyl-D-valine), BOC--L-phenylalanine, BOC-L-isoleucine, BOC-L-alanine, N-3,5-dinitrobenzoyl-D-phenylglycine, N-3,5-dinitrobenzoyl-L-leucine, 3,5-dinitrobenzoyl chloride, all from Sigma (St. Louis, MO, U.S.A.). The 4-aminobutyldimethylmethoxysilane reagent used to bond the amino acid to porous silica was purchased from Petrarch System (Bristol, PA, U.S.A.). All the amino acid bonded phases were synthesized in our laboratory[10].

All solvents were from J. T. Baker (Phillipsburg, NJ, U.S.A.) and were re-

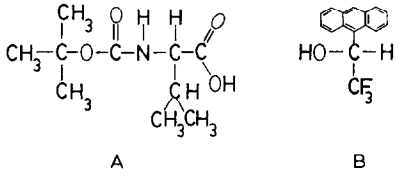

Fig. 1. Structural formulas of (A) butoxycarbonyl-D-valine (BOC-D-Val) and (B) 2,2,2-Trifluoro-1-(9-anthryl)ethanol (TFAE).

agent-grade, HPLC-grade or better unless otherwise stated. All the deuterated solvents ^2H_2O, C^2HCl_3, $C^2H_2Cl_2$, cyclohexane-d_{12} were purchased from Aldrich (Milwaukee, WI, U.S.A.).

The *R*(−) and *S*(+) forms of 2,2,2-trifluoro-1-(9-anthryl)ethanol used as test solutes were purchased from Sigma.

Preparation of N-(3,5-dinitrobenzoyl) amino acids. The procedure of Pirkle and Finn[11] was used in which a slurry of 2 mol of amino acid and 2 mol of 3,5-dinitrobenzoyl chloride in 2 l of dry tetrahydrofuran (THF) were stirred at room temperature for 7–10 days. Unreacted amino acid was removed by filtration and washed with THF. The filtrate was concentrated under vacuum, and the residue dissolved in saturated sodium bicarbonate solution and extracted continuously with diethyl ether to remove neutral impurities. The pH of the solution was adjusted to 5.3 with citric acid, and the liberated N-(3,5-dinitrobenzoyl) amino acid was extracted with diethyl ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated to dryness. The yield of crystalline derivative was 60–80%. The derivatives of amino acid were sent for elemental analyses, and there was a very good agreement between the found and calculated percentages of carbon, hydrogen and nitrogen.

Preparation of the methyl ester of N-(3,5-dinitrobenzoyl) amino acids. N-(3,5-Dinitrobenzoyl) amino acid (0.2 mol) was esterified with 0.22 mol of thionyl chloride and 60 ml of methanol. The reaction was carried out according to the procedure of Zaoral *et al.*[12]. The methyl ester hydrochloride was neutralized with 10% sodium bicarbonate solution and the methyl ester 3,5-dinitrobenzoyl amino acid recrystallized from diethyl ether. The products were sent out for carbon, hydrogen and nitrogen elemental analyses and very good agreement was found between calculated and experimental values.

Instruments

All of the ^{13}C and ^1H solution-state NMR spectra were recorded using either a FX90Q or a FX270 FT-NMR spectrometer (JEOL, Tokyo, Japan). The FX-90Q has a 2.12 tesla electromagnet and operates at 22.6 MHz for ^{13}C, whereas the FX270 has a 6.35 tesla super-conducting magnet and operates at 67.8 MHz for ^{13}C. Both spectrometers are equipped with a TI-980B computer (64K, 16 bit) system. The FX270 is also equipped with a variable temperature device for the sample. All of the solid-state ^{13}C spectra were obtained using the FX270 high-field instrument equipped with a high power amplifier system provided by Chemagnetics (Fort Collins, CO, U.S.A.). The magic angle spinning solid-state probe used in the super-conducting magnet system was also of Chemagnetics design. This probe was of a single-coil, double-tuned, single air-bearing, single air-drive design, the details of which are proprietary.

Procedures

Solid–liquid suspension NMR. These ^{13}C NMR experiment were conducted on 0.8–1.0 g of stationary phase synthesized in our laboratory[10]. The stationary phase was weighed directly into a 10-mm NMR sample tube. Approximately 5–6.0 ml of the desired mixture of solvents was added and the tube hand-shaken until proper mixing was obtained. A 5-mm NMR tube containing the locking solvent was then

carefully inserted into the sample tube. The tube was ultrasonicated for 30 s to 1 min to remove trapped air. The sample was allowed to stand for 24 h before the NMR analysis was run.

Each ^{13}C NMR spectrum was a result of the accumulation of 20000 scans unless otherwise stated. The irradiating radio frequency pulse width was adjusted to about a 45° flip angle. The pulse was followed by a 1.9-ms predelay and a 0.2785-s acquisition time; the post delay was 2.0 s. Any variations in these pulse sequences are noted. All the spectra were broad-band decoupled. All the chemical shifts reported are with reference to tetramethylsilane (TMS).

The stationary phases were rejuvenated after each use according to the procedure recommended by Zwier and Burk[13]. The packing was filtered through a sintered glass filter funnel, collected and washed with five 25-ml portions of filtered methanol. The washed packing was dried overnight at 100–110°C under vacuum.

Solution-state NMR. The NMR spectra of the pure amino acid derivative, spacer, and test solutes were normally obtained by dissolving the pure solid in appropriate solvents. All of the ^{13}C spectra were obtained using a 10-mm NMR tube and a standard 45° pulse-observewait sequence with a waiting period of 1–5 s. Internal deuterated solvent was used as a locking agent.

All ^{1}H spectra were obtained by dissolving the pure material in appropriate deuterated solvents in a 5-mm tube. The same pulse sequence, with a 90° pulse instead of 45° pulse, was used.

The ^{19}F NMR spectra of the TFAE solutes were taken in exactly the same way as ^{1}H NMR spectra in a deuterated solvent. The typical spectral width of 5500 Hz was used. Chemical shifts were measured with reference to monochlorodifluoromethane which has resonance at 0.0 ppm.

The ^{13}C and ^{1}H spectra for chiral stationary phase and chiral solute interaction in different solvents were obtained in exactly the same way as the solution-state NMR. The 1:1 quantities of the sorbent and sorbate were at a concentration of $1 \cdot 10^{-3}$ *M* in all the experiments, unless otherwise noted. The temperature at which the experiments were run, usually 28°C, was kept constant within ±0.2°C.

The same kind of interaction study was done on amino acid derivatized silica. A 1:1 molar ratio of "active" surface species and of adsorbate were mixed in a 10-mm NMR tube and ^{13}C spectra were recorded as described earlier.

Solid-state ^{13}C NMR. The solid-state ^{13}C NMR spectra of the bonded amino acid packings were obtained using a magic angle spinning solid-state probe. A basic cross-polarization technique was used which is explained in greater detail in ref. 14.

A bullet-type rotor made of Kel-F [poly(trifluorochloroethylene)], about 0.4-ml capacity, was tightly packed with the solid sample. Poly(dimethylsilane), which has a resonance at −1.7 ppm compared to TMS was used as an internal reference. Precise determination of the spinning rate was done by looking at the potassium bromide side bands which were introduced into the spectrum. Then, in order to obtain spectra without spinning side bands, a technique called total side-band suppression (TOSS) was used[15].

RESULTS

Preliminary studies of derivatized silica packings

Derivatized amino acid or dipeptide packings were synthesized by reacting the protected amino acid or dipeptide derivatives with δ-aminobutyl silanized silica[10].

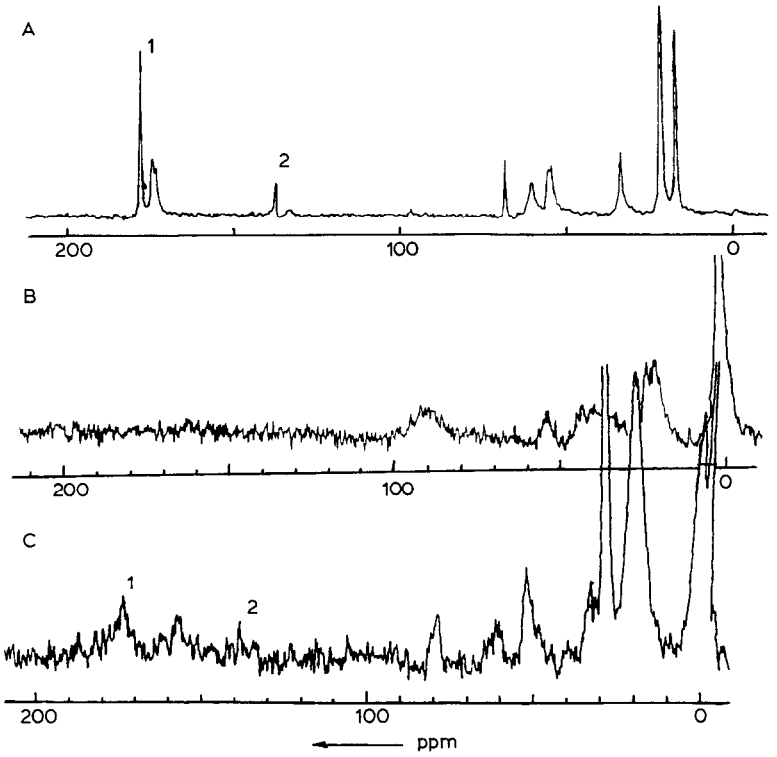

Fig. 2. ^{13}C CP-MAS spectra of (A) L-alanine–L-valine crystalline solid, (B) γ-Aminobutyl silanized silica, (C) L-alanine–L-valine dipeptide bonded to silica gel.

Definite proof that the derivative of the amino acid was chemically bonded to the porous silica gel through a spacer, was done by comparison of its ^{13}C resonance signals with those from the individual molecules used in the syntheses. Thus, the CP-MAS ^{13}C NMR spectra of the derivatized packings were compared with those of the dissolved or crystalline amino acid derivative spectra and with the silanized silica gel spectra in order to confirm the nature of the solid stationary phases.

A typical comparison is shown in Fig. 2. Fig. 2A corresponds to ^{13}C CP-MAS spectra of L-alanine-L-valine dipeptide; Fig. 2B and C corresponds, respectively, to the δ-aminobutyl silanized silica and the dipeptide bonded through that spacer to silica. It is clear from the figure that the C=O resonances (peaks 1 and 2) of the pure dipeptide closely corresponded to the C=O resonances of the dipeptide bonded phase. In addition, the $-CH_3$ resonances of the dipeptide and $-CH_2$ resonances of the δ-aminobutyl spacer also closely corresponded to those of the dipeptide bonded phase.

Similarly, ^{13}C CP-MAS NMR comparisons were also done for other amino acid packings synthesized in our laboratory[10]. Fig. 3 shows a ^{13}C CP-MAS NMR of BOC-L-Val bonded to silica. The C=O resonances at 172.48 and 156.87 ppm closely corresponded to the C=O resonances of pure BOC-L-Val suggesting positive

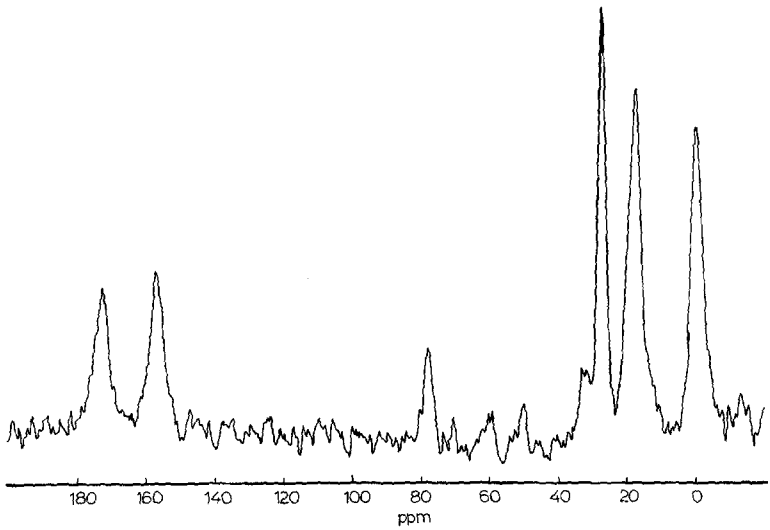

Fig. 3. ^{13}C CP-MAS spectra of BOC-L-Val derivatized silica.

identification. In addition, the carbon, hydrogen and nitrogen elemental analyses and carbon coverage data further supported the NMR information about the derivatized solid surfaces.

The main disadvantage of CP-MASS studies is that they are usually carried out in the absence of solvent and, therefore, do not represent the actual liquid chromatographic conditions. Therefore, conventional solution FT-NMR studies have been conducted on surfaces modified by amino acid derivatives by measuring suspensions of the packings in different solvents.

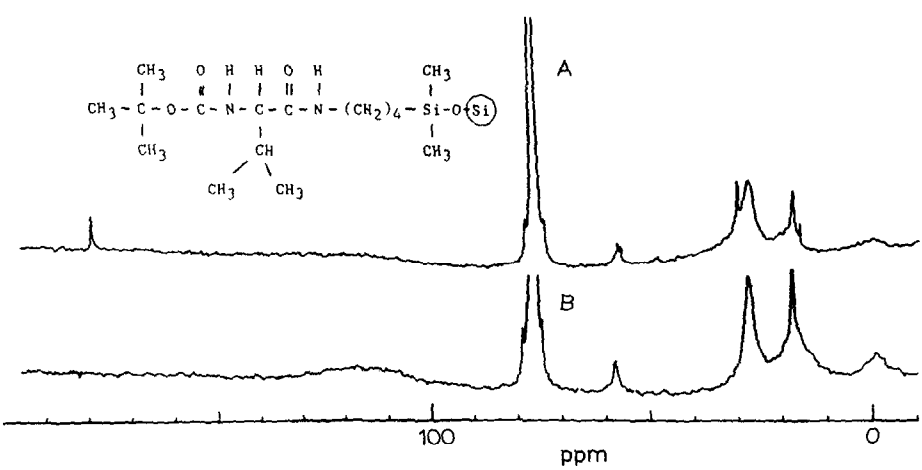

Fig. 4. ^{13}C "High-resolution" NMR spectra of suspensions in chloroform of (A) BOC-D-Val and (B) "deBOC"-D-Val.

"deBOC" study. Fig. 4 shows a ^{13}C NMR comparison involving a BOC-D-Val packing before and after removal of the BOC group. The packing materials were suspended in chloroform and ^{13}C NMR spectra obtained. The most important aspect to note is the presence of a C=O resonance in Fig. 4A at about 175.0 ppm. When compared with the spectrum obtained using the "deBOC" D-Val, Fig. 4B, the absence of the C=O peak from the latter was noted. This confirmed the effectiveness of the procedure for removal of the BOC group. Because no enantiomeric separation was observed on the "deBOC" packing, the importance of the protecting group for the chiral separation was indicated.

Solvent study. Similar "high-resolution" solution NMR studies of the BOC-D-Val bonded phases were carried out in different solvents. When a ^{13}C NMR spectrum of a BOC-D-Val packing was obtained in water–methanol (95:5), the absence of the C=O resonance was noted as was the peak broadening for the methyl and methylene resonances. Then, ^{13}C NMR of the packing was also run in pure methylene chloride and in a hexane–methylene chloride (80:20) mixture. In both cases, the presence of the C=O peak was noted. These different solvents were tried because pure chloroform and pure methylene chloride were found to be chromatographically strong solvents, that is, no measureable chromatographic retention was observed for TFAE. Hexane–methylene chloride (80:20) was then examined by NMR because enantiomeric separation was observed in this solvent system. Unfortunately, due to the extra carbons of hexane, most of the information was hidden by the ^{13}C resonances for the solvent. For that reason, cyclohexane–methylene chloride (80:20) was tested chromatographically and found to be nearly equivalent. Its NMR spectrum was simpler and, therefore, advantageous to use.

^{1}H and ^{13}C NMR studies of bonding interactions: BOC-D-Val and R- or S-TFAE

^{1}H and ^{13}C NMR chemical-shift differences were observed when pure BOC-D-Val was mixed with *R*- or *S*-TFAE. These chemical shifts were measured in different solvents: chloroform, methylene chloride and cyclohexane–methylene chloride (80:20). Pure chloroform and pure methylene chloride were tried because the reso-

TABLE I

NMR SENSES OF NONEQUIVALENCE (Δppm)* FOR MIXTURES IN DIFFERENT SOLVENTS OF BOC-D-VALINE WITH *R*(−)-, OR *S*(+)-TFAE

Solvents	*BOC-D-Val alone (ppm)***	*Chemical shift*	
		Mixed with R(−)-TFAE (Δppm)	*Mixed with S(+)-TFAE (Δppm)*
Chloroform	C=O (177.09)	−1.83	−0.97
	N–H (5.84)	−0.18	−0.10
Methylene chloride	C=O (176.71)	−0.02	+0.18
	N–H (5.99)	−0.12	−0.05
Methylene chloride–cyclohexane (20:80)	C=O (177.95)	−0.64	−0.21
	N–H (6.84)	−0.60	−0.53

* Nonequivalence (Δppm) is the difference from homomolecular to heteromolecular association.

** Values in parentheses represent the homomolecular solution shifts in the respective solvents.

TABLE II

EFFECT OF STRUCTURAL CHANGES WITHIN THE AMINO ACIDS ON THE α VALUES AND THE NMR SENSES OF NON-EQUIVALENCE FOR N-3,5-DINITROBENZOYL AMINO ACID DERIVATIVES AND *R* (−)- *VERSUS S*(+)-TFAE IN CYCLOHEXANE–METHYLENE CHLORIDE (1:1)

(H) = High field shift; (L) = low field shift.

Amino acid	*C=O*	*N–H*	$\alpha = k'_2/k'_1$
3,5-DNB-D-phenylglycine	0.450 (H)	0.610 (L)	1.65
3,5-DNB-L-leucine	0.380 (H)	0.410 (L)	1.45
3,5-DNB-D-valine	0.278 (H)	0.358 (L)	1.33

nances of the carbonyl and NH groups, which gave the only significant differences in chemical shifts, were readily observed in these solvents. Changes in line shape and multiplicity were observed for the anthryl group on TFAE upon association with solvents. Table I shows the differences in chemical shifts for the C=O and N–H group of BOC-D-Val in the presence of *R*- and *S*-TFAE in these solvents. It is clearly seen from the table that the chemical shifts for *R*-TFAE were greater in most cases than *S*-TFAE, suggesting that *R* interacts more with BOC-D-Val than *S* enantiomer. Similar information was obtained from a chromatographic study, that *R* is retained

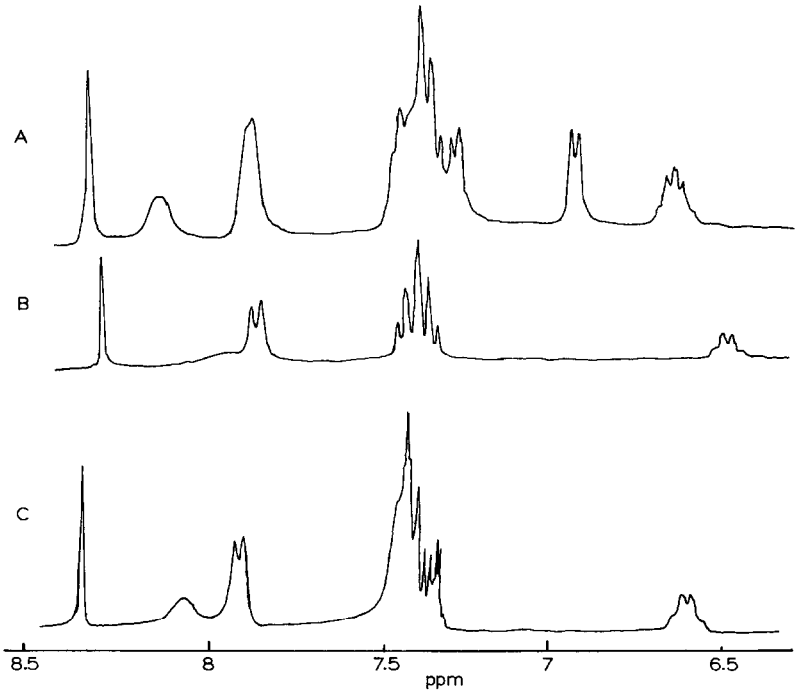

Fig. 5. ^{1}H NMR of the aromatic region of (A) 3,5-DNB-D-phenylglycine mixed with *R*-TFAE, (B) TFAE, (C) 3,5-DNB-D-phenylglycine mixed with *S*-TFAE.

longer than *S* enantiomer. We have also observed that, as one increases the percentage of methylene chloride in hexane (and presumably in cyclohexane), the capacity factor (k') values for the enantiomers decrease but the α value remains the same. These facts suggest that, in this particular case, the solvent is not participating in or interfering with the chiral recognition mechanism.

BOC-L-phenylalanine and R- or S-TFAE. We have observed that there is an absolute difference in the chemical shifts for the mixture compared to the pure species. However, the differences in shift between the *R* and *S* mixtures was negligible. This correlates well with our chromatographic study in which we found that the TFAE enantiomers could not be separated on a BOC-L-phenylalanine packing in the hexane–methylene chloride (80:20) solvent system.

N-3,5-Dinitrobenzoyl amino acid derivatives and R- or S-TFAE. Pirkle[11] has observed that by changing the amino acid structure, the α value for TFAE changed. Table II shows the change in α value on going from phenylglycine to leucine to valine. For that reason, we measured ^1H and ^{13}C NMR chemical-shift differences when a pure 3,5-DNB amino acid derivative was mixed with *R*- or *S*-TFAE. Table II shows chemical-shift non-equivalences between the *R* and *S* isomers of TFAE when they were mixed with different amino acid derivatives. It can be clearly seen that the chemical shift differences also change in the same order as the α values. However, it is not a simple linear relationship. The fact that a non-chiral interaction is also involved is undoubtedly important. For that reason an attempt was made to measure the corresponding ^{13}C chemical shifts when the species was adsorbed.

BOC-D-Val derivatized silica and R- or S-TFAE interaction ^{13}C NMR study. A sorbate–sorbent interaction study was carried out by suspending about 1.0 g of BOC-D-Val silica and a molar equivalent amount of TFAE corresponding to the surface active species concentration and capacity factor of the test solute. The brief investigation showed that the C=O resonances of the BOC-D-Val were observed but no signals from the TFAE were observed. Besides that, no significant difference in chemical shifts between *R*- or *S*-TFAE was observed. In this preliminary study, it was observed that significant amount of TFAE was adsorbed on to the silica surface.

DISCUSSION

In the case of BOC-D-Val the differences in chemical shifts for the two enantiomers of TFAE when mixed with BOC-D-Val were very significant for the C=O and N–H of the BOC-D-Val. In addition, it was noticed that the presence of BOC protecting group was important for the fractionation of *R* and *S* isomers of TFAE. It can also be noticed from Table I that the *R* enantiomer of TFAE interacts more strongly or is favored more than the *S* enantiomer. These data were found to be in perfect agreement with the chromatographic retention behavior, where the *R* enantiomer is retained longer on BOC-D-Val than *S* enantiomer.

At this point of time, it should be kept in mind that a direct allocation of enantioselectivity based on the knowledge of differences in stability between diastereomeric associated complexes in pure solution state is not always the only contributing factor towards the selectivity. The silica gel surface holding the BOC-D-Val chiral graft is involved not only in the overall retention process but also it may have

some effect(s) on enantioselectivity. Hence, it is very important that one measures the differences in chemical shifts for the *R* and *S* enantiomers of TFAE in contact with BOC-D-Val (spacer) derivatized silica packing.

It must be noted at this point that the hydrogen-donation of the –OH on TFAE upon association interaction with BOC-D-Val was observed but unfortunately it was not possible to measure accurately the differences in the chemical shift for this –OH on TFAE.

In the present study more attention was given to the differences in chemical shift of the C=O and N–H groups of the amino acid for obvious reasons, but along with these changes the other changes observed were in the line shape and multiplicity for the anthryl side chain of pure TFAE upon association with chloroform and methylene chloride. As pointed out by a reviewer of this paper, the different band shapes stem from the restricted rotation of the substituent in the 9-position owing to the steric impediment of the flanking *peri* hydrogens that are nonidentical in the slow exchange limit. That exchange rate will be affected by the solvent. As shown in Fig. 5, definite changes in chemical shift were also observed for the anthryl group of TFAE upon association with 3,5-DNB derivatives of the amino acids, indicating a possible third site of interaction. In spite of the large changes in the peak shapes at about 7.5 ppm, it is very interesting to note that the mean value of the chemical shifts was not very different for the three: A, 7.360; B, 7.385; C, 7.394. In addition, the peak at 6.8 ppm in spectrum A is clearly missing from spectrum C. However, the reduced scale for C is deceiving because the integrated area for the peak at 7.5 ppm is correspondingly greater than the 7.5-ppm peak in spectrum A.

An attempt was also made to examine the fluorine shifts to see if they were interacting. Unfortunately, no significant differences in chemical shifts for the $-CF_3$ group of TFAE was observed when it was interacting with the BOC-D-Val CSPs.

In addition to all these enantioselective interactions there are some non-chiral contributions as well. It has been observed by Roumeliotis *et al.*[16] and Pirkle and Hyun[17] that when different lengths of methylene group spacer were used to prepare CSPs having the same chiral species, somewhat different α values were observed for a given racemic pair of test solutes. The differences in α values presumably reflect either assistance or interference with the chiral recognition retention mechanism by the spacer. The presence of residual silanol groups on the silica surface may also be a possible source of this additional retention.

CONCLUSIONS

The results shown here demonstrate differences in chemical shifts for the C=O and N–H group of BOC-D-Val, in the presence of *R* or *S* enantiomers of TFAE, indicated that there are two important points of interaction. Changes in line shape, and differences in chemical shift for the anthryl group suggested a third point of interaction. In the system studied, the loss of the protecting BOC group affected the chromatographic separation of the two isomers. Changing the structure at the chiral carbon of the stationary phase decreased the differential interaction as well as the α value.

Further experiments are in progress that test the "non-chiral" contribution

from the silica surface on which the amino acid is bonded. In addition, an attempted correlation between the α value and the difference in chemical shifts for different derivatives of amino acids are under active investigation.

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