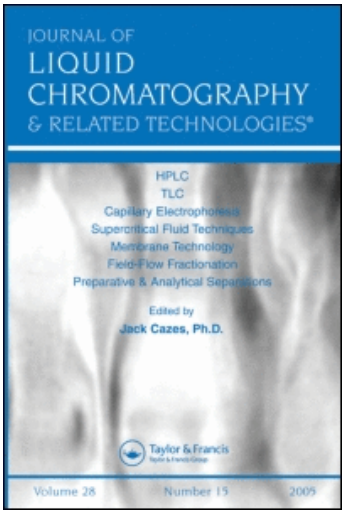

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CHARACTERIZATION OF ORGANO-MAGNESIUM MODIFIED KEL-F POLYMERS AS COLUMN PACKINGS

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ABSTRACT

The reactivity of Kel-F (polychlorotrifluoroethylene) with a variety of Grignard reagents and the HPLC separation capability of these modified packings have been compared. Columns packed with long alkyl (C-8 or C-18) modified Kel-F 6061 supports had poor lifetimes while short alkyl (CH_3) modified fluoropolymers did not produce effective separations. Aromatic modified Kel-F 6300 polymers, particularly phenyl supports, were both pressure stable and useful for the retention of various functionalized aromatics as well as the separation of simple drug mixtures.

INTRODUCTION

The fluorocarbon polymer Kel-F (polychlorotrifluoroethylene) has several advantageous properties as a candidate for reversed-

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phase HPLC column packings. First, like most fluorocarbon polymers, Kel-F is extremely inert and is not degraded by common oxidizing and reducing agents as well as solutions extreme in pH. The surface of Kel-F is uniformly hydrophobic and is considered even more nonpolar than hydrocarbons. In addition, Kel-F particles have sufficient hardness in packed columns to withstand typical pressure drops encountered in HPLC. This is in contrast to Teflon which is quite soft. Finally, the polymer is commercially available in bulk and is not extremely expensive. However, in particulate form, Kel-F is considered to be nonporous resulting in a low surface area (about 1.5 m^2/g). To alleviate this shortcoming while at the same time modifing the surface of the polymer, we have discovered that organolithium reagents will functionalize Kel-F by displacement of the chlorine with a variety of functional groups (1). Methyl-, butyl-, and phenyl-lithium have all led to the facile preparation of the corresponding derivatized polymer and the latter two have been studied in some detail as HPLC column packings (2,3). However, these three organolithium compounds are the main ones commercially available and the synthesis of organolithium reagents is not particularly straightforward in practice.

To expand the variety of functionalized Kel-F polymers for potential analytical use, we have explored the modification of the fluoropolymer with organomagnesium or Grignard reagents which are more easily synthesized. Although the reactivity of Kel-F with organomagnesium compounds has been briefly described elsewhere

(1), HPLC characterization of the so-modified Kel-F particles packed in columns has not been reported. Both of the following polymers, Kel-F 6061 (100% chlorotrifluoroethylene) and Kel-F 6300 (97% chlorotrifluoroethylene-3% vinylidene fluoride), were considered. Previously it had been concluded that organolithium reacted Kel-F 6300 was modified too extensively and was no longer pressure stable during routine HPLC column use (2). However, Grignard reagents, being weaker reducing agents, were thought to be more appropriate for the derivatization of Kel-F 6300. The methyl-, phenyl-, and naphthyl-Kel-F 6300 polymers were synthesized and compared as HPLC packings. Further study was focused on phenyl Kel-F 6300 because of the higher coverage and better separation capability. Besides the measurement of the reduced plate height and capacity factors for various functionalized aromatics, application of this packing for the separation of simple drug formulations was demonstrated.

MATERIALS AND METHODS

Materials

Kel-F 6300 (100-200 mesh) was provided as a gift from the 3M Company (Minneapolis, MN) while the Kel-F 6061 (80-100 mesh) was obtained from A. M. Plastics (Rockaway, NJ). The particles were ground to less than 44μm as described previously (2). During elutriation, collection of particles between about 15-30 μm was carried out.

Methylmagnesium bromide (3M in diethyl ether) and gold-label tetrahydrofuran (THF) were obtained from Aldrich Chemical Co.

(Milwaukee, WI). All other chemicals were obtained from a variety of sources and were reagent grade or better.

Kel-F Modification and Subsequent Characterization

Grignard-modified Kel-F particles were synthesized as follows. About 0.2 moles of the desired alkyl or aryl bromide was refluxed with an equivalent amount of magnesium metal in 125 mL of degassed THF for about 45 minutes or until the metal had disappeared. The above solution or 0.2 moles of CH_3MgBr was added dropwise to 7 grams of Kel-F (0.06 moles) in 125 mL of degassed THF and the mixture allowed to reflux for about 1-3 hours. Because the reactions proceeded readily, this time interval was more than sufficient. The reaction solutions were quenched by the slow addition of 10-20 mL of methanol. The product was filtered and washed with 100-200 mL portions of methanol, 2 M HCl, acetone, hexane, and methanol. The dry derivatized polymeric particles appeared unchanged except for a color change from white to gold-brown. Infrared spectra were recorded on a Perkin-Elmer Model 683 spectrophotometer and the elemental analyses were carried out by either Galbraith or Atlantic Microlab. The ESCA spectra were taken with a Hewlett-Packard 5950A spectrometer equipped with a monochromatic Al X-ray source (1370.8 eV) set at 600 watts.

Chromatography

The stainless steel columns (150 x 4.1 mm i.d.) were slurry-packed in methanol at a pressure of 34.5 MPa (6.9 MPa = 1000 psi) by a Model 10-600-30 pneumatic amplifier pump (S.C. Hydraulic Engineering Corp. Los Angeles, CA) and a high pressure slurry

packer (Alltech, Deerfield, IL.). Before packing, repetitive sedimentation of the reacted Kel-F polymers in methanol was carried out in a graduated cylinder to remove fines. Two other columns used were a 5 μm C-18 silica column, 25 cm long, obtained from IBM Instruments (Danbury, CT) and a 10 μm PRP-1 column, 15 cm long, from the Hamilton Co. (Reno, NV). All separations were carried out using a Milton Roy Model 396-57 minipump (LDC, Riviera Beach, FL) equipped with a Rheodyne Model 7010 injector (Rheodyne, Berkeley, CA). The detector was an Altex Model 153 fixed wavelength (254 nm) UV detector (Altex, Berkeley, CA). Peaks were recorded by an Omniscribe Model B-5000 recorder (Houston Instruments, Austin, TX).

RESULTS AND DISCUSSION

Reactivity of Kel-F Polymers

Infrared spectrometry proved to be very useful for the qualitative characterization of the reacted Kel-F. In the region of 3000-2800 cm^{-1}, the Kel-F IR spectrum had no absorption bands due to the absence of C-H bonds in the structure. However, spectra of the alkyl and aromatic derivatized polymers showed definite peaks below and above 3000 cm^{-1}, respectively. In addition, the intensity of the C-Cl stretch at 950 cm^{-1} was markedly diminished.

Elemental analysis was carried out to more clearly gain quantitative information regarding the degree of functionalization of the Kel-F polymers (Table 1).

For all the modified Kel-F polymers, the elemental analyses certainly confirmed the IR results of substitution and loss in Cl.

TABLE 1. Elemental Analyses for Kel-F - Organomagnesium Reactions.

Grignard	Kel-F Type	%C	%H	%Cl
none	6061 or 6300	21.3	0.0	29.4
CH_3	6061	40.9	2.4	7.0
C_8	6061	57.6	6.4	4.1
C_{18}	6061	65.5	8.8	3.4
CH_3	6300	42.5	3.4	1.0
Phenyl	6300	48.1	1.9	10.4
Naphthyl	6300	40.1	2.1	12.2

No significant loss in fluorine was noted for either the methyl Kel-F 6061 or 6300 polymer as evidenced by respective %F values of 48.3 and 47.6. The total elemental sum for these functionalized polymers were found to be 98.6 and 94.5% respectively, indicating the substitution reaction was the primary one and not elimination. The greater reactivity of Kel-F 6300 with CH_3MgBr as compared to Kel-F 6061 was a general trend and expected due to the decreased crystallinity of a copolymer and resultant lower hardness.

The ESCA spectra also confirmed the higher functional group surface coverage of Kel-F 6300 as compared to Kel-F 6061 (Fig. 1). The carbon electron (Cl) binding energy profile showed two peaks for underivatized Kel-F 6300. The main peak at 291 eV corresponded to carbons in a fluorinated environment, CF_2 and CFCl. The slight broadening of the low binding energy side of this peak was caused by the chemical shift of CF_2 adjacent to CH_2. The peak at 284 eV corresponded to the methylene group within each vinylidene fluoride

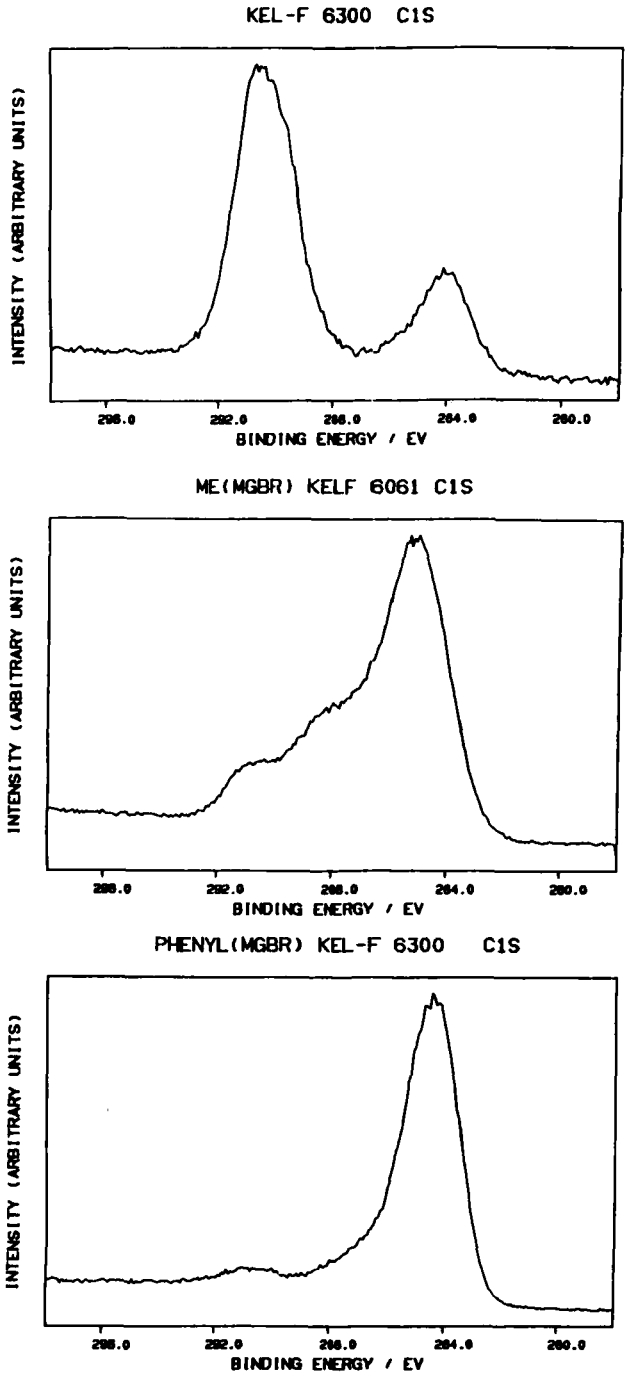

FIGURE 1. Carbon 1s ESCA spectra of Kel-F 6300, methyl MgBr Kel-F 6061, and phenyl MgBr Kel-F 6300.

monomer. For the Kel-F 6061 ESCA spectrum, only the peak at 291 eV was evident as expected. In contrast, the C1 spectrum for methyl Grignard reacted Kel-F 6061 showed three distinct peaks. The peak at 291 eV was due to the CF_2 or CFCl moieties as before and the shoulder at 288 eV was assigned to oxidized carbon or the CF carbon linked to the CH_3 group. The large peak at 285 eV was due to the methyl carbon. Other Grignard modified Kel-F 6061 polymers such as octyl or butyl types provided similar spectra. Because fully halogenated carbons were still evident by ESCA, surface coverage must be somewhat spotty. On the other hand, the ESCA spectrum of the phenyl Kel-F 6300 polymer showed only a primary peak at 285 eV due to the phenyl carbons. This peak possessed a slight tail on the high energy binding side indicating some exposed oxidized or CF carbons. However, the peak at 291 eV was very small giving evidence that coverage of the polymer surface was quite uniform.

Another trend that can be pointed out in Table 1 is the decreased functionalization with increasing group bulkiness for both Kel-F 6061 and 6300 reacted polymers. For example, the mmoles of substituent/g Kel-F calculated using a previously described procedure (3) for C-8 Kel-F 6061 was 4.6, about twice that for C-18 Kel-F 6061. The estimated functionalization of the naphthyl Kel-F 6300 polymer was also less than the phenyl Kel-F 6300 polymer.

Chromatography

The separation of aniline, N-ethylaniline, N,N-dimethylaniline, and N,N-diethylaniline on silica packings can be difficult due to the basic nature of these compounds. Their respective pKa

values are 4.6, 5.1, 5.1, and 6.6. In particular, N,N-diethylaniline can be irreversibly adsorbed on C-18 silica through interaction with isolated acidic silanols (4). This set of anilines was chosen as a test mixture for various Grignard modified Kel-F packings. Representative chromatograms generated on columns packed with CH_3MgBr, C-8 MgBr, and C-18 MgBr modified Kel-F 6061 particles are shown in Figure 2. The separation was unsatisfactory using the CH_3-modified packing perhaps due to the very short functional group. The other two Kel-F derivatives produced quite good separations however column lifetimes were short. At even a low flow rate of 0.3 ml/min, pressures of approximately 2500 psi were obtained for these long chain alkyl columns. Attempts at removing fines by furthur sedimentation and sieving followed by repacking did not improve column performance. This pressure problem was probably due to the presence of the long alkyl chains on the Kel-F surface and not extreme etching of the polymer caused by the Grignard reaction. The C-8 and C-18 modified Kel-F particles compacted together when rubbed between the thumb and forefinger but the plain Kel-F or CH_3-modified Kel-F particles did not.

Focus of the chromatographic performance of aryl Kel-F 6300 polymers was initiated at this point due to the previously described limitations of Kel-F 6061 and the greater reactivity of the 6300 copolymer. The separation of a mixture of p-nitroaniline, toluene, and phenanthrene was compared on the phenyl Kel-F 6300, the naphthyl Kel-F 6300, and the methyl Kel-F 6300 columns as shown in Figure 3. Again, the methyl column was inferior with no

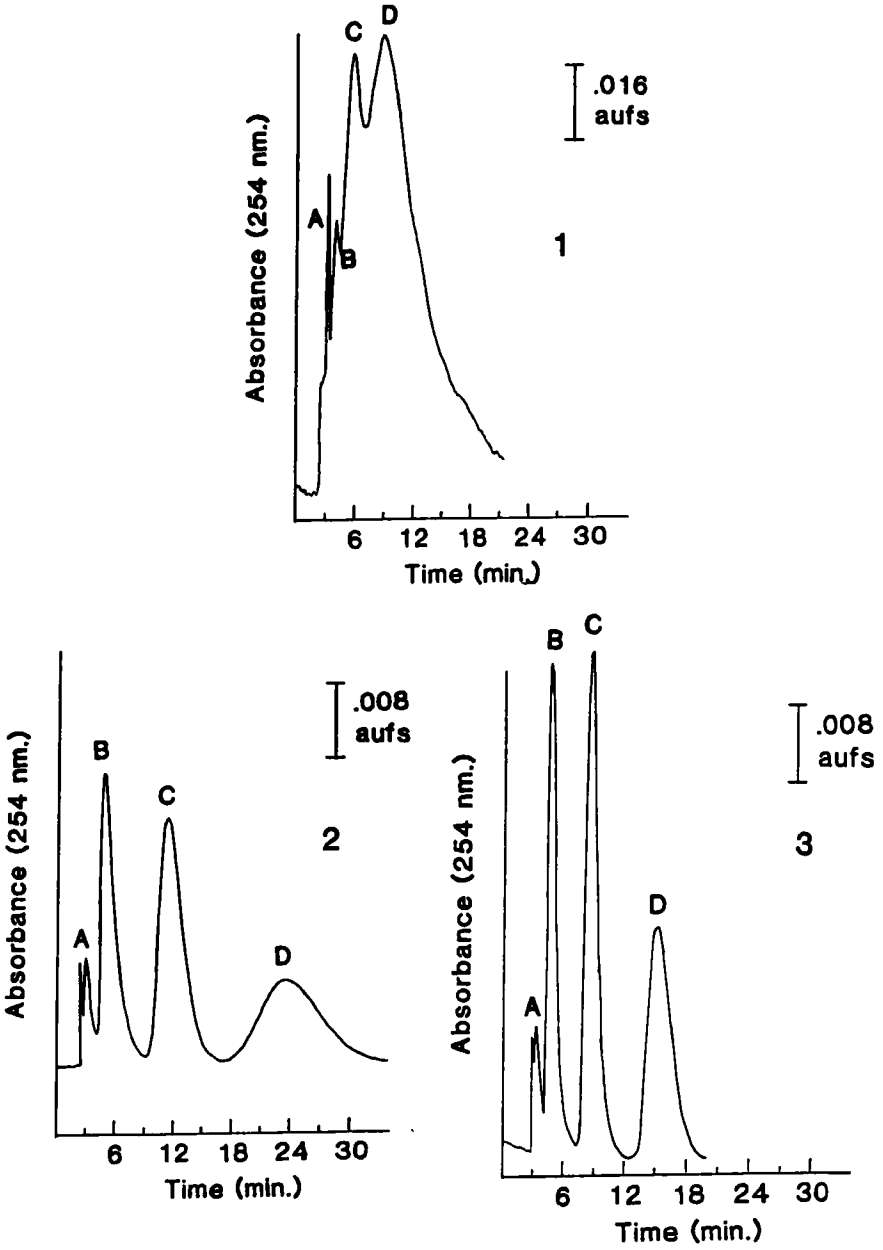

FIGURE 2. Separation of aniline (A), N-ethylaniline (B), N,N-dimethylaniline (C), and N,N-diethylaniline (D) on CH_3-MgBr (1), C-8 MgBr (2), and C-18 MgBr (3) modified Kel-F 6061. All solute concentrations were 50 μgm/ml. Mobile phase: 83:17 methanol- H_2O. Flow rate: 0.3 ml/min.

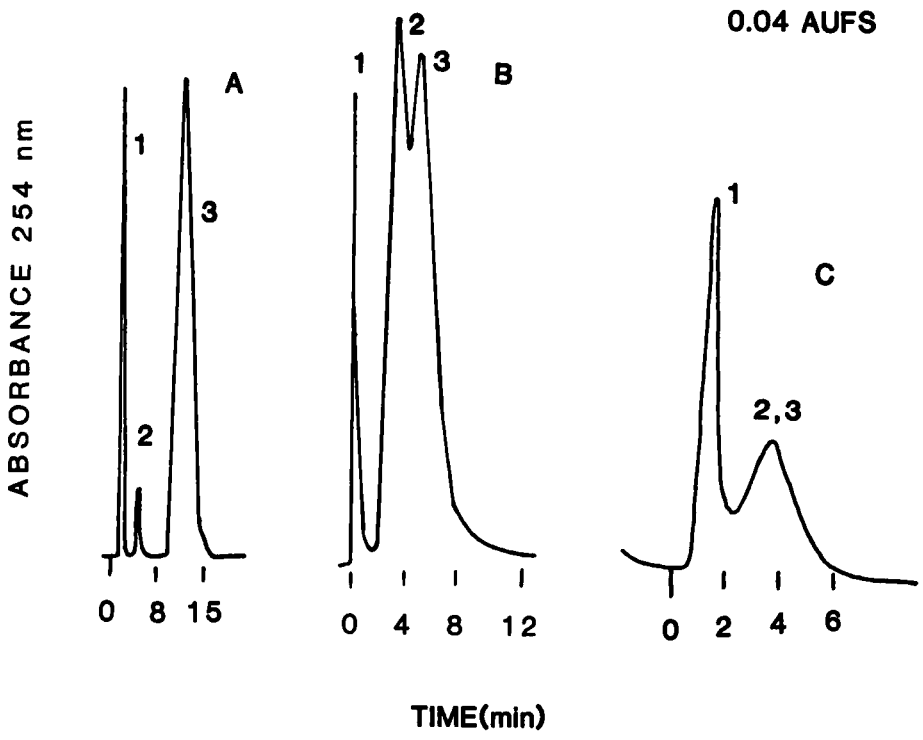

FIGURE 3. Separation of p-nitroaniline (1), toluene (2), and phenanthrene (3) on phenyl-MgBr (A), naphthyl-MgBr (B), and methyl-MgBr (C) modified Kel-F 6300. Mobile phase: 80:20 acetonitrile-H_2O. Flow rate: 1 ml/min.

resolution of toluene and phenanthrene in the latter peak. The phenyl and naphthyl columns retained the sample components longer due to enhanced π-to-π interactions. Of the two, the phenyl column was superior with respect to resolution and peak shape probably because of the lower coverage of the naphthyl groups. The better separation of polar aromatics such as the N-alkyl substituted anilines for the phenyl column as compared to the naphthyl column

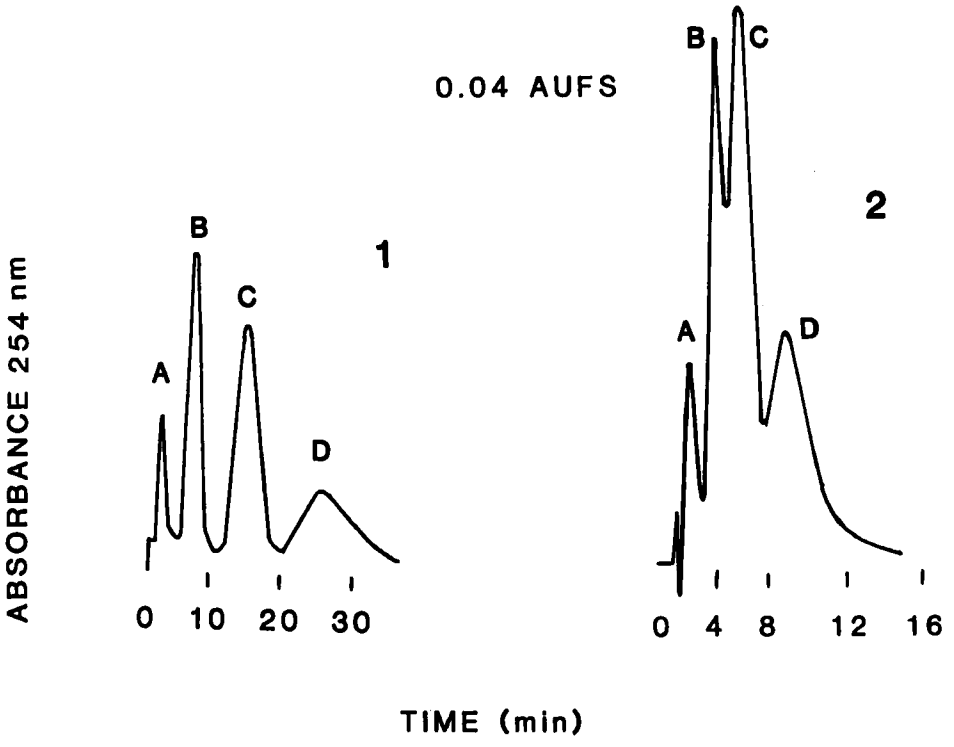

FIGURE 4. Separation of the same aniline mixture as in Figure 1 on phenyl-MgBr (1) and naphthyl-MgBr (2) modified Kel-F 6300. Mobile phase: 60:40 acetonitrile-H_2O. Flow rate: 1 ml/min.

is again seen in Figure 4. Therefore, emphasis on the further characterization of phenyl Kel-F 6300 was made. Using biphenyl as the solute, a minimum HETP value of 1.09 mm corresponding to 5500 plates/m was calculated. The optimum mobile phase flow rate was found to be 0.65 ml/min. Considering the surface area of phenyl Kel-F 6300 had only increased to 4 m^2/g and the somewhat wide particle size range, these values were not unreasonable.

TABLE 2. Capacity Factor (k') Data for Substituted Benzenes Using Various HPLC Packings and a 30:70 Acetonitrile-Water Mobile Phase.

Functional Group	Kel-F 6300	Phenyl Kel-F 6300	C-18 Silica	PRP-1 Polymer
$-CONH_2$	0	0.50	0.44	0.86
$-CH_2OH$	0	1.25	1.03	2.4
$-NH_2$	0	2.49	1.4	4.5
-CHO	0	9.50	4.4	15.0
$-CH_2NH_2$	0	10.7	5.2	16.0
-CN	0.38	11.8	4.2	16.0
$-NO_2$	0.92	32.5	6.3	31.0
$-OCH_3$	0.85	41.0	8.25	37.0
-H	1.18	42.2	8.21	37.0

The hydrophobic selectivity of Grignard phenyl Kel-F 6300 for a variety of functionalized benzenes was compared to that data for unmodified Kel-F 6300, C-18 silica, and PRP-1 in Table 2.

Several points can be made when comparing the data for the four different column materials. First, the retention order of these compounds on all four packings was essentially identical indicating the dominant retention mechanism was hydrophobic in nature. Second, modification of Kel-F was clearly important as shown by zero or very little retention for plain Kel-F 6300. Third, the phenyl Kel-F column gave higher k' values than the C-18 silica column. This may be due to the uniform hydrophobic surface of Kel-F as compared to C-18 silica which likely has

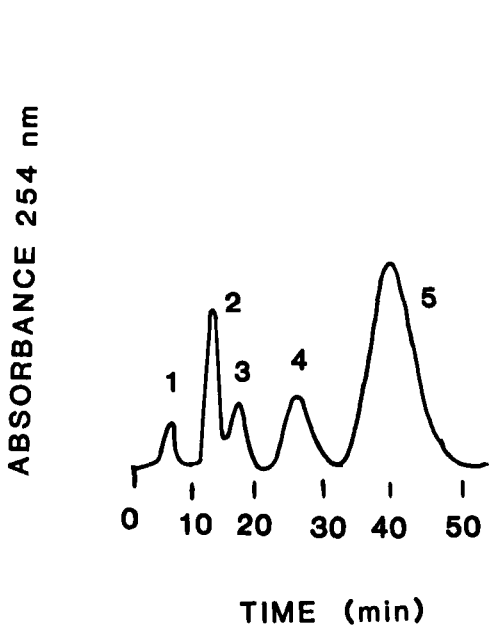

FIGURE 5. Separation of benzene (1), toluene (2), biphenyl (3), naphthalene (4), and phenanthrene (5). Mobile phase: 86:14 methanol-H_2O. Flow rate: 0.8 ml/min. Absorbance units full scale (AUFS) = 0.04.

accessible silanols. Finally, the capacity factor data for phenyl Kel-F 6300 and PRP-1 were roughly comparable and were particularly high for nitrobenzene, anisole, and benzene. It seems quite feasible that phenyl Kel-F could be suited for the preconcentration of these particular trace organics as well as polyaromatic hydrocarbons from water.

Various applications using the phenyl-MgBr Kel-F column have been explored. The separation of a variety of aromatic and polyaromatic solutes using an isocratic methanol-water mobile phase

is shown in Figure 5. Simple drug mixtures and tablet formulations were also assayed using this Grignard-modified fluoropolymer. Hydrazinophthalazine (hydralazine) and hydrochlorothiazide, a diuetic, are often combined in drug mixtures for the treatment of hypertension. Two pharmaceutical tablets, each tablet containing 50 mg of each drug, were sonicated in a 50-50 water-methanol solution and brought to volume in a 250 ml volumetric flask. The resultant separation is shown in Figure 6. Because of the lower molar absorptivity of hydralazine, an absorbance scale change at 4 minutes was required. Possible interfering substances such as dyes were not a problem. In addition, it was possible to follow the degradation with time of hydralazine to phthalazine in water by separation of the two components in about 14 minutes using a 50:50 acetonitrile-H_2O mobile phase. Similarily, the determination of 1,8-dihydroxyanthraquinone (Danthron) in laxative tablets was easily accompolished by HPLC using this column.

The versatility of using Grignard reagents for the modification of Kel-F to prepare specifically tailored polymers has been demonstrated here and should be possible to extend even furthur. Clearly smaller particles and an improvement of the particle distribution of Grignard-modified Kel-F packings are needed to improve column efficiency. Elutriation steps using a small capacity sedimentation pipet both before and after reaction should solve the particle distribution problem. Jet milling of Kel-F powder as currently done is expensive and does not generate much material less than 20 μm. Commercial availability of Kel-F

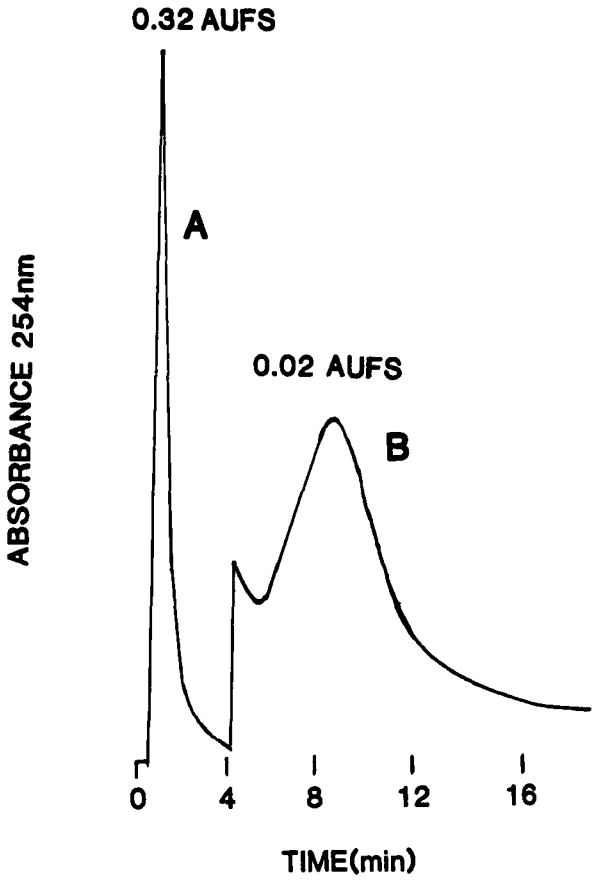

FIGURE 6. Separation of hydrochlorothiazide (A) and hydralazine (B). Mobile phase: 50:50 methanol-H_2O. Flow rate: 2.5 ml/min. The baseline change at 4 minutes marks an AUFS change from 0.32 to 0.02.

6061 or 6300 particles in the 5-15 μm range is really required to permit extension of analytical applications.

ACKNOWLEDGMENTS

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