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Determination of Enantiomeric *N*-Trifluoroacetyl-L-prolyl Chloride Amphetamine Derivatives by Capillary Gas Chromatography/Mass Spectrometry with Chiral and Achiral Stationary Phases

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***d*- and *l*-Amphetamine mixtures were derivatized with *N*-trifluoroacetyl-L-prolyl chloride (L-TPC) and then determined by a chiral and an achiral phase capillary gas chromatograph/mass spectrometer system. The total resolution of four possible isomers by the chiral column facilitates the determination of enantiomeric impurities in the commercial L-TPC and *d*- and *l*-amphetamine used for this study. The mean values and standard deviations are 5.19, 2.11, 2.78 and 0.93, 0.23, 0.36, respectively. With the purity of L-TPC determined, the enantiomeric ratio of *d*- and *l*-amphetamine in each test solution was also determined by an achiral column. Results were compared to that obtained by the chiral column and by calculation and were found to be statistically nondifferent at the 95% confidence level.**

A recent court ruling (*1*) requiring the identification of a specific drug enantiomer has created a unique challenge to the forensic science analytical community. Specific nuclear magnetic resonance spectrometric methods have been developed for the determination of amphetamine (*2*), methamphetamine (*3*), and cocaine enantiomers (*4, 5*), to meet this challenge. The gas chromatography/mass spectrometric (GC/MS) methods developed here will have the advantages of wider instrument availability, versatility, and practicality.

Due to differences in biological activity, the differentiation of *d*- and *l*-amphetamine has always been a topic of considerable interest in clinical studies. Among various methods used for enantiomeric analysis (*6*), the gas–liquid chromatographic (GLC) method is superior, in most cases, for quantitative determinations (*7, 8*). With the implementation of a mass spectrometer as the detector for GLC analysis, qualitative identification is easily achieved.

Gas–liquid chromatographic separation of enantiomers can be achieved by employing either chiral or achiral stationary phases (*9*). The latter approach requires prior derivatization with a chiral reagent to convert enantiomers to isolatable diastereomers; the former approach achieves the desired separation on the basis of in situ formation of transient diastereomers between the chiral stationary phase and substrate. However, to increase the stability and volatility of substrates, prior derivatization with an achiral derivatizing reagent is generally required even though enantiomers are separated by chiral stationary phases.

Earlier works on the GLC analysis of enantiomers have been reviewed (*9*). Recent representative references are summarized in Table I. The analyses of drug enantiomers were almost exclusively performed on packed achiral (conventional) columns following prior derivatization with chiral reagents. Since the development of the first chiral stationary phase (*28*), a variety of chiral phases (*29–31*) have been subsequently introduced. Recently, two chiral columns were made commerically available. These chiral phases, coated on open tubular glass capillary columns, have been used extensively for the separation of amino acid enantiomers.

The combination of using a chiral derivatizing reagent with a chiral stationary phase has been briefly investigated (*27*) in the determination of amino acid enantiomers. It was qualitatively concluded that the use of a chiral stationary phase can avoid the inaccuracy introduced when impure chiral derivatizing reagents are used. Theoretical considerations on the interaction of chiral stationary phases with substrates have been discussed in several studies (*32–36*). The work presented here will concentrate on a comparison of a chiral and achiral column for the determination of TPC-derivatized amphetamine enantiomers. The procedure described here depends on a reasonable assumption that racemization at the concerned chiral centers does not occur during the entire analytical process. Further discussion concerning racemization is treated in selected references (*21, 37*).

EXPERIMENTAL SECTION

Apparatus. A Varian MAT 112S/MAT SS166/SS144 (Bremen, West Germany) and a Hewlett-Packard HP-5985 (Palo Alto, CA) gas chromatograph/mass spectrometer/data system (GC/MS/DS) were used for this study. A 25-m (0.30 mm i.d.) glass Chirasil-Val from Applied Science (State College, PA), and a 25-m (0.20 mm i.d.) fused silica glass SP-2100 column from Hewlett-Packard (Avondale, PA) were used for this study.

Reagents. *d*- and *l*-Amphetamine were obtained from Aldrich Chemical Co. (Milwaukee, WI). The chiral derivatizing reagent, 0.1 M *N*-trifluoroacetyl-L-prolyl chloride (TPC) in chloroform, was purchased from Regis Chemical Co. (Morton Grove, IL). The manufacturer reports a 6% contamination of D-TPC. All chemicals were kept dry and cool and were used without further purification.

Procedure. The standard TPC derivatization procedure recommended by the supplier was adopted to form the diastereomeric pair *N*-(trifluoroacetyl-L-prolyl-*d,l*-amphetamine. A typical derivatization started with the addition of 15 μL of neutralized *d*-, *l*-, or *d,l*-amphetamine to 0.50 mL of chloroform in a pressure acylation tube followed by the addition of 1.0 mL of the TPC reagent. The mixture was allowed to stand for 5 min before the addition of 20 μL of triethylamine to take up excess unreacted TPC. After 15 min of intermittent shaking, 1.0 mL of 6 N HCl was used to remove the ammonium salt. The mixture was finally washed with 1 mL of distilled water and then dried over anhydrous magnesium sulfate before dilution and analysis. A slight variation in procedure was used for the derivatization of the illicit amphetamine preparation. A 0.20-g pulverized sample from an illicit tablet was dissolved in 8.0 mL of 0.10 N NaOH. The solution was centrifuged to remove insoluble adulterants. The supernatant was extracted with 30 mL of chloroform three times. The organic layers were combined, dried with magnesium sulfate, filtered, and then evaporated to 0.50 mL under dry nitrogen. The 0.50-mL aliquot was subsequently used for TPC derivatization as described previously for control samples.

The mass spectrometer was operated in electron impact mode at 70 eV. The source temperature was maintained at 200 °C. Spectra were collected in the range m/e = 45–450 and in most cases started at 10 min after injection. The gas chromatographic starting temperature, final temperature, programming rate, and

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Table I. A Review on the GLC Analysis of Enantiomers

stationary phase	chiral (C), achiral (A)	column type	compds analyzed	derivatizing reagent	ref
EGA	A	packed	amines	TPC	10
OV-275	A	packed	amphetamine	*N*-pentafluoro-*S*-(−)prolyl-*l*-imidazolide	
OV-17	A	packed	amines	(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl Cl	12, 13
OV-1, OV-17	A	packed	hydroxyamines	(*R*)-α-phenylbutyric acid	14
SE-30, OV-17	A	packed	phenylalkylamines and amino acids	(+)-α-phenylbutyric acid and related compds	15
SE-30	A	packed	β-arylethylamines	α-methyl-α-methoxypentafluorophenylacetic acid	16
SE-30	A	packed	amphetamine	TPC	17, 18
SE-30, DEGS Carbowax 20M	A	packed	amines	TPC and related compds	19
N,N'-[2,4-(6-ethoxy-1,3,5-triazine)diyl]bis(L-valyl-L-valine)isopropyl ester	C	capillary	amines	TPC, *N*-pentafluoropropionic anhydride (PFPA)	20
neopentyl glycol adipate	A	capillary	leucine	TPC	21
Chirasil-Val	C	capillary	amino acids, amino alcohols	PFPA	22–25
RSL-007 (*l*-valine-*tert*-butylamide/polycyanopropylmethyl phenylmethyl silicone)	C	capillary	amino acids	PFPA, trifluoroacetic anhydride, heptafluorobutyric anhydride	26
N-trifluoroacetyl-*l*-phenylalanyl-*l*-aspartic acid-bis(cyclohexyl) ester	C	capillary	amino acids	PFPA	27

linear velocity for SP-2100 and Chirasil-Val columns were as follows: 100 °C, 220 °C, 10 °C/min, 28 cm/s; and 150 °C, 180 °C, 5 °C/min, 44 cm/s, respectively. Temperature was held at the starting temperature for 1 min and at the final temperature for 10 min for both columns. Helium was used as the carrier gas throughout all experiments. The inlet pressure was maintained at 40 psi.

RESULTS AND DISCUSSION

Figure 1 shows reconstructed chromatograms of representative samples analyzed by the two columns. Since impurities are normally encountered in illicit samples, as shown in Figure 1b, single ion chromatograms (Figure 1c) are added to clearly display amphetamine peaks. This common application should facilitate qualitative and quantitative analyses of "street grade" samples. It is clearly demonstrated that *d*- and *l*-amphetamine can be separated and identified by the described GC/MS procedure. Although separation of *d*- and *l*-amphetamine has been carried out previously (*11–13, 17, 18*) with the use of packed achiral columns, the work described here employs capillary columns to improve efficiency and achieve better resolution as discussed below.

One significant advantage in using the chiral column is that the four possible isomers resulting from the reaction of *d*- and *l*-amphetamine with D- and L-TPC are completely resolved. This is important because commercial TPC contains a small amount of D-TPC. The elution order of these four isomers in increasing retention time is *d*-amphetamine–D-TPC (*SR*), *l*-amphetamine–L-TPC (*RS*), *l*-amphetamine–D-TPC (*RR*), and *d*-amphetamine–L-TPC (*SS*) (*d*-amphetamine and L-TPC are designated by the "S" configuration while *l*-amphetamine and D-TPC are designated by the "R" configuration). The assignments of these four peaks in a chromatogram were based on relative peak sizes. Since the purity of the TPC reagent is supplied by the manufacturer and the relative concentrations of *d*- and *l*-amphetamine in control samples are known, the relative intensities of *SR*, *RS*, *RR*, and *SS* are predictable and their respective peaks are assigned accordingly.

The ability of the chiral column to resolve the four resulting isomers is used to determine the contamination of the TPC reagent by the small amount of D-TPC. A series of *d,l*-amphetamine mixtures were derivatized with the TPC reagent and submitted to GC/MS analysis. The percentage of D-TPC is measured by dividing the peak area of *SR* by that of the sum of *SR* and *SS*; or by dividing the peak area of *RR* by that of the sum of *RR* and *RS*. The peak areas are based on total ion and single ions 166, 194, and 237 (see Figure 2 for the fragments of these ions). Results are presented in Table II. When a low concentration of *l*-amphetamine (relative to *d*-amphetamine) is used, the peak area of *RR* is small; similarly, when a low concentration of *d*-amphetamine is used, the peak area of *SR* is small. To avoid inaccuracy caused by the measurement of small peak areas, we did not use calculations involving these small areas and they are omitted from Table II. The grand mean value of D-TPC calculated from Table II is 5.19% (standard deviation 0.93%), which is close to the

Table II. Determination of Percent D-TPC in the Commercial TPC Reagent Using the Chirasil-Val Column

amphetamine ratio (*d*:*l*)[a]	method for calculation[b]	% D-TPC total ion	166	194	237
100:0	1/(1 + 4)	4.82	5.60	5.44	4.97
90:10	1/(1 + 4)	5.00	6.10	5.38	5.70
75:25	1/(1 + 4)	4.47	5.73	5.22	4.90
	3/(2 + 3)	3.90	6.12	5.30	4.48
60:40	1/(1 + 4)	4.65	5.90	5.41	5.15
	3/(2 + 3)	4.74	6.12	5.75	4.94
50:50	1/(1 + 4)	2.84	4.25	3.10	3.08
	3/(2 + 3)	6.18	7.17	7.10	6.81
40:60	1/(1 + 4)	3.72	5.30	4.73	4.57
	3/(2 + 3)	5.30	5.69	5.60	5.40
25:75	1/(1 + 4)	3.33	5.10	4.20	4.00
10:90	3/(2 + 3)	5.50	5.28	6.30	6.08
0:100	3/(2 + 3)	5.21	5.72	6.26	5.44

[a] Numbers in this column represent the relative volumes of commercial *d*- and *l*-amphetamine used; due to the presence of enantiomeric impurities, they do not represent true concentration ratios. [b] 1, 2, 3, and 4 are peak areas for *SR*, *RS*, *RR*, and *SS*, respectively.

Table III. Calculation of Enantiomeric Impurities in Commercial *d*- and *l*-Amphetamine

amphetamine sample	peak	area and % impurity					
		total ion	166	194	237	av	std dev
d-	*RS* (2)	1208	473	155	159		
	SS (4)	63117	19920	6621	8094		
	2/(2 + 4)	1.88	2.32	2.29	1.93	2.11	0.23
l-	*SS* (4)	1235	530	176	185		
	RS (2)	52389	16521	5778	6553		
	4/(2 + 4)	2.30	3.11	2.96	2.75	2.78	0.36

Table IV. Observed Peak Areas and Quantity vs. Response Correlations of TPC Derivatized *d*- and *l*-Amphetamine Obtained from the Analysis on the Chirasil-Val Column

ng of amphetamine injected (*d*:*l*)	area (*d*:*l*)			
	total ion	166	194	237
89.4:1.9	63117:1208	19920:473	6621:155	8094:159
88.7:11.6	50103:6293	16079:2229	5277:743	6410:857
71.1:24.9	40937:13729	13119:4571	4356:1573	5274:1833
54.5:36.8	32804:22809	10114:7285	3495:2523	4165:3000
38.9:38.7	28696:24697	8951:8061	3252:2817	3778:3283
38.8:57.1	26306:42778	8240:13595	2817:4772	3365:5551
25.2:70.8	14911:39760	4937:12919	1671:4210	1992:4856
10.8:80.5	6762:49014	2283:14880	772:5196	851:6035
2.7:93.2	1235:52389	530:16521	176:5778	185:6553
intercept	389, 889	193, 550	149, 178	85.9, 240
slope	622, 589	196, 182	64.5, 62.9	79.4, 72.1
correlation	0.982, 0.983	0.984, 0.983	0.979, 0.979	0.980, 0.976

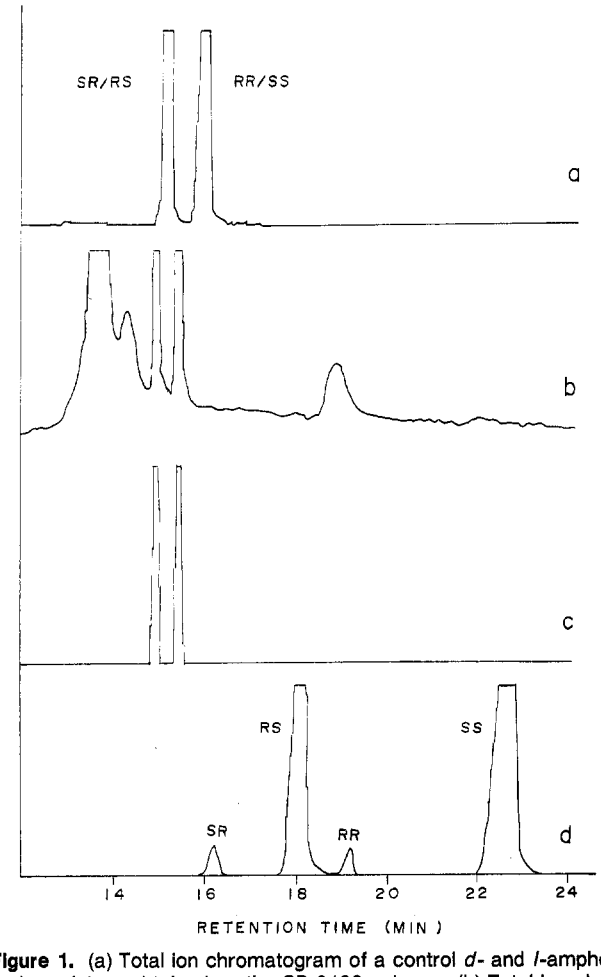

Figure 1. (a) Total ion chromatogram of a control *d*- and *l*-amphetamine mixture obtained on the SP-2100 column. (b) Total ion chromatogram of illicit amphetamine obtained on the SP-2100 column. (c) Single ion (*m*/*e* = 237) chromatogram of illicit amphetamine obtained on the SP-2100 column. (d) Total ion chromatogram of the control *d*- and *l*-amphetamine mixture obtained on the Chirasil-Val column.

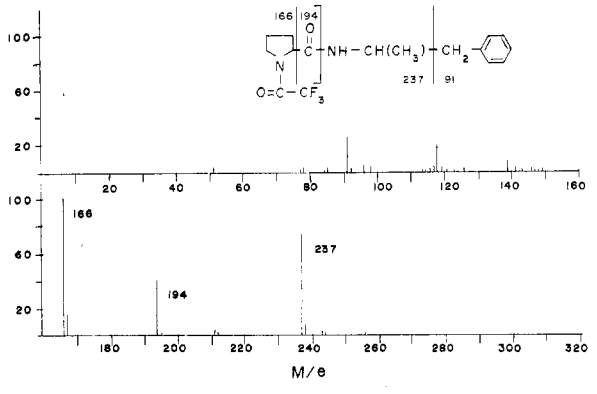

Figure 2. Mass spectrum of TPC-derivatized amphetamine.

6% reported by the manufacturer.

The ability of the chiral column to resolve these four isomers is further utilized to determine the purities of commerical *d*- and *l*-amphetamine. To simplify the calculation, only samples containing unmixed *d*- and *l*-amphetamine were used. To calculate the contamination of *l*-amphetamine in the unmixed *d*-amphetamine, the peak area of *RS* is divided by that of the sum of *RS* and *SS*. Similarly, to calculate the contamination of *d*-amphetamine in the unmixed *l*-amphetamine, the peak area of *SS* is divided by that of the sum of *SS* and *RS*. Due to their low intensities, peak areas of *RR* and *SR* were not used. Using data presented in Table III, the percentages of the respective impure enantiomer found in the commercial *d*- and *l*-amphetamine are 2.11% (standard deviation 0.23%) and 2.78% (standard deviation 0.36%).

Once the purities of L-TPC and *d*- and *l*-amphetamine used are known, the exact quantities of *d*- and *l*-amphetamine used in each injection are calculated. The performances of the two stationary phases are evaluated. Peak areas of *RS* and *SS* obtained from the Chirasil-Val column are summarized in Table IV and plotted in Figure 3. Since the peak areas for *RR* and *SR* are generally small and less accurate, they are not used in this study.

Table V. Corrected Peak Areas of TPC Derivatized *d*- and *l*-Amphetamine Obtained from the Analysis on the SP-2100 Column

ng of amphetamine injected (*d*:*l*)	area (*d*:*l*)			
	total ion	166	194	237
88.8:11.6	194978:30430	55808:8413	18850:3018	21439:3607
77.8:27.3	134383:51486	36046:14867	12401:4425	12568:5515
60.0:40.5	110982:78407	31146:21555	9752:7851	11477:8042
45.7:45.6	99905:79136	29072:23029	8673:7265	9961:8077
35.1:51.6	66098:111108	17967:31665	6788:11411	7864:12457
23.9:67.5	50578:123829	14153:35334	4690:12490	5736:14043
10.8:80.5	18763:133781	5802:38487	1821:13225	2193:15640

Table VI. Comparison of the *d*/*l* Amphetamine Ratios Obtained by Calculation and Measurements from the Two Columns

calcd (*d*/*l*)		7.60	2.85	1.48	1.00	0.68	0.35	0.13
Chirasil-Val	TI	7.96	2.98	1.44	1.16	0.61	0.38	0.14
	166	7.20	2.87	1.39	1.11	0.61	0.38	0.15
	194	7.10	2.77	1.39	1.15	0.59	0.39	0.15
	237	7.50	2.88	1.39	1.15	0.60	0.41	0.14
	av	7.44	2.88	1.40	1.14	0.60	0.39	0.15
	std dev	0.386	0.086	0.025	0.022	0.009	0.014	0.006
SP-2100 (corrected for enantiomeric TPC impurity)	TI	6.40	2.61	1.42	1.26	0.59	0.40	0.14
	166	6.60	2.42	1.44	1.26	0.57	0.40	0.15
	194	6.25	2.80	1.24	1.19	0.59	0.38	0.14
	237	5.94	2.28	1.43	1.23	0.63	0.41	0.14
	av	6.30	2.53	1.38	1.24	0.60	0.40	0.14
	std dev	0.278	0.226	0.095	0.033	0.025	0.013	0.005
SP-2100 (without correction for enantiomeric TPC impurity)	TI	4.78	2.34	1.37	1.23	0.63	0.45	0.19
	166	4.91	2.19	1.39	1.23	0.60	0.44	0.20
	194	4.67	2.48	1.21	1.17	0.63	0.42	0.19
	237	4.53	2.08	1.38	1.21	0.67	0.45	0.19
	av	4.72	2.27	1.34	1.21	0.63	0.44	0.19
	std dev	0.162	0.175	0.085	0.028	0.029	0.014	0.005
% error		37.9	20.4	9.5	21.0	7.4	25.7	46.2

Corresponding data obtained from the SP-2100 column are summarized in Table V. Since *SS* and *RR* and *RS* and *SR* are enantiomers to each other and not resolved by the achiral column, only two peaks are observed. By observing the relative intensity of these two peaks, it is concluded that the *SR*/*RS* pair elutes first. The peak areas contained in the body of Table V have been corrected for the small amount of the other enantiomer coeluted by using the following equations.

$$A_d = A(A_{d,a} - D)/(A - D)$$

$$A_l = A(A_{l,a} - D)/(A - D)$$

where A_d and A_l are the corrected areas for *d*- and *l*-amphetamine, respectively, $A_{d,a}$ and $A_{l,a}$ are the apparent areas of *d*- and *l*-amphetamine obtained from the chromatograms, $A = (A_{d,a} + A_{l,a})/2$, and D is the impurity of D-TPC in units of peak area and is given by $D = 5.19/100 \times (A_{d,a} + A_{l,a})$. The *d*/*l* amphetamine ratios obtained by calculation and by measurements from both columns are listed in the first three blocks of Table VI. Statistical analysis (analysis of variance) of average values obtained by these two columns indicate that there is no significant difference at the 95% confidence level. The *d*/*l* amphetamine ratios obtained from the analysis on the SP-2100 column without correction for the D-TPC impurity are listed in the fourth block of Table VI. The percent errors are listed in the last row of this table.

In conclusion, the results reported here indicate that both chiral and achiral (conventional) columns can be used for enantiomeric composition determination. Chiral columns possess the advantage of being able to resolve all isomers, and direct calculation of enantiomeric composition is possible. However, the peak multiplicity resulting from chiral columns in combination with a chiral reagent may cause peak overlapping and difficulties in chromatogram interpretation for analyses of "street grade" samples where the presence of several other chromatographic peaks is common. In cases where an achiral column is used, correction for the coelution of the other enantiomer is needed if the chiral derivatizing reagent is impure. This difficulty may become a serious

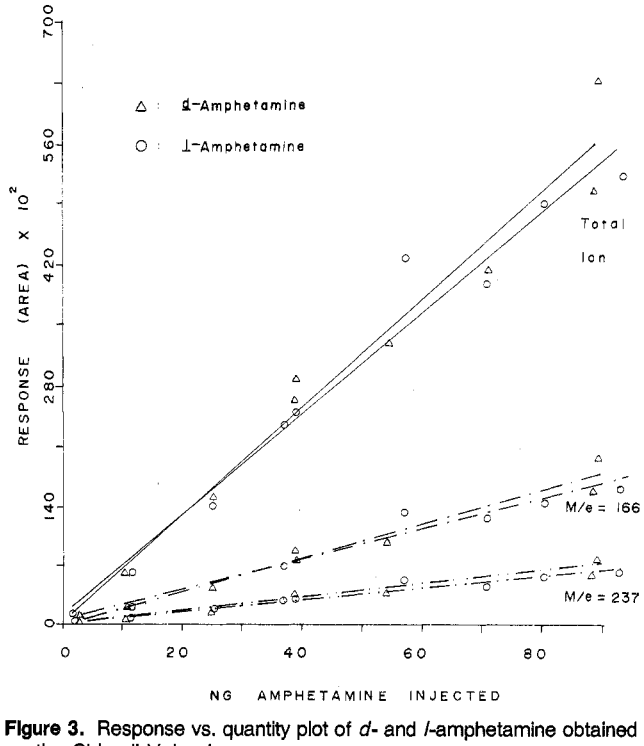

Figure 3. Response vs. quantity plot of *d*- and *l*-amphetamine obtained on the Chirasil-Val column.

problem if the exact enantiomeric purity of the derivatizing reagent is not available.

ACKNOWLEDGMENT

The authors thank the Research Resources Center, Univerity of Illinois at the Medical Center, and the USEPA Central Regional Laboratory, Chicago, IL, for the use of their GC/MS facilities.

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RECEIVED for review April 29, 1981. Accepted July 24, 1981.

Calculation of Linear Temperature Programmed Capillary Gas Chromatographic Retention Indices of Polycyclic Aromatic Compounds

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Capillary column gas chromatographic retention indices of polycyclic aromatic compounds (PAC) can be calculated by using descriptors derived from the structures of the solute molecules. The retention indices of 231 PAC from the literature were regressed against a set of calculated molecular structure descriptors, and a four-variable equation was found with a multiple correlation coefficient of 0.990. The variables included in the model are consistent with qualitative observations made during the experimental measurements of the retention indices.

Polycyclic aromatic compounds (PAC) comprise the largest class of known chemical carcinogens. Their widespread presence throughout our environment as products of incomplete combustion of organic materials make their identification and determination an important analytical problem. Capillary column gas chromatography is a technique commonly used for the analysis of mixtures containing PAC (*1*). A retention index system for linear temperature programmed gas chromatography (GC) of PAC has recently been described in the literature (*2*) along with reported retention index data for a large number of PAC (*3, 4*). Retention indices are widely used as a standardized method for reporting retention data. Retention indices can be used as an aid for tentative identification of chromatographic peaks within one laboratory as well as interlaboratory comparisons where pure reference materials may not be available.

Chromatographic retention for capillary column gas chromatography is the measured quantity which represents the interactions between gas-phase solute molecules and the stationary liquid phase of the chromatographic system. The strength of the interactions, and ultimately the retention index, depends upon the identities of the solute molecules. The retention of the homologous series of alkanes is known to increase in an exponential relationship with the number of carbon atoms comprising the alkyl chain. This series of hydrocarbons is used as the internal standards for measuring Kovats retention indices. The relationships between molecular structure and chromatographic retention are not always known.

Studies of quantitative structure–activity relationships (QSAR) investigate the relationships between the molecular structures of organic compounds and their biological activities. Structure–activity studies are based on the premise that relationships exist between numerical quantities (descriptors) used to represent molecular features and the biological ac-

0003-2700/81/0353-2184$01.25/0 © 1981 American Chemical Society