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Chiral separations of indan, tetralin and benzosuberan derivatives by capillary electrophoresis

Kyung-Hyun Gahm, Jauh-Tzuoh Lee, Lisa W. Chang, Daniel W. Armstrong*

Department of Chemistry, University of Missouri-Rolla, Rolla, MO 65401, USA

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Abstract

Several indan, tetralin and benzosuberan derivatives of diverse polarities were enantio-resolved by the use of sulfated β-cyclodextrins (CDs) or mixtures of sulfated β-CDs and γ-CD as chiral additives in capillary electrophoresis. Mixtures of sulfated β-CDs and hydroxypropyl β-CDs were also successfully utilized for enantiomeric and diastereomeric separations of some of the tetralin derivatives with two stereogenic centers. Both neutral and anionic analytes were resolved in the reversed electrophoretic polarity mode. Cationic amino derivatives of indan and tetralin were enantio-resolved in the conventional electrophoretic polarity mode.

Keywords: Enantiomer separation; Indan derivatives; Tetralin derivatives; Benzosuberan derivatives

1. Introduction

Various alkyl-, oxygen- or nitrogen-containing aromatic hydrocarbons have been identified in coal, oil shale and crude oil [1–5]. Among them, derivatives of hopane, sterane, indan, tetralin and various isoprenoids have been regarded as biological markers (biomarkers) because the molecular structure of these compounds resembles the structural subunits of biological precursors, such as lipids, steroids and porphyrins which occur in the source materials [6,7]. Hydroaromatic compounds have been used to study the source, maturation, migration and biodegradation of crude oils [8–11]. Since some of these compounds are chiral, they have been recognized as potential chiral biomarkers of geochemical importance, e.g., in shale, crude oil and coal [12,13].

Nitrogen- or oxygen-containing derivatives of tetralin, indan and benzosuberan are important synthetic intermediates for a variety of chiral and achiral organic compounds [14–20]. For example, α-tetralone has been used to prepare 7,7-dioxo-14-oxa-7γ-thiadibenzo[*a,j*]anthracene-2,12-disulfonic acid [15], β-keto esters, heterocyclic spiroazeridines [16], thermorubin, a potent antibiotic substance [17], and a variety of other compounds [18,19]. There are a large number of important pharmacological compounds that are derivatives of oxygenated aminotetralins [21,22]. For example, 8-hydroxy-2-(di-*n*-propylamino)tetralin is a selective serotonin (5-hydroxytryptamine, 5-HT) receptor agonist [21]. Also, (*R*)-7-OH-dipropylaminotetralin seems to be a selective dopamine D_3-agonist [22].

Our on-going research for chiral biomarkers in coal and crude oil necessitated the synthesis of alkyl derivatives of indan, tetralin and benzosuberan to be used as standards, since these compounds are not readily available commercially. Detailed information

*Corresponding author.

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on the synthesis, identification and GC enantioseparation of these compounds was given elsewhere [23]. Most of these compounds are uncharged and do not have appreciable solubility in water. Consequently, they are not amenable to direct analysis by ordinary capillary electrophoresis. However, use of proper chiral additives can enhance the solubilization of these compounds and provide mobility and/or chiral recognition.

Recently, we reported the successful application of dual (neutral and charged) CD mixtures of sulfated β-CDs and native α-CD as chiral additives in the reversed polarity electrophoretic mode to achieve enantiomeric separations of monoterpenes [24]. The addition of α-CD to the running electrolyte which contained sulfated β-CDs imparted differences in the mobilities of these monoterpenes, resulting in remarkable enantioseparations. There was no resolution of these compounds with sulfated β-CDs alone. Besides mixtures of α-CD and sulfated β-CDs, the combination of sulfated β-CDs and the larger γ-CD is a possible alternative. Mixtures of sulfated β-CDs with hydroxypropyl β-CDs have not yet been employed, but may also be a successful combination.

The first use of mixtures of charged and neutral cyclodextrins to achieve or enhance CE enantioseparations was by Anigbogu et al. [25]. General reviews on the separation of enantiomers by CE have been published [26,27].

In the present study, enantioresolutions of several newly synthesized racemic derivatives of tetralin, indan and benzosuberan by a capillary electrophoretic technique are reported. Resolutions of the analytes were explored by using mixtures of different charge or size CDs as capillary electrophoresis run buffer chiral additives.

2. Experimental

2.1. Materials

Sulfated β-CDs (average degree of substitution, four) were obtained from American Maize products (Hammond, IN, USA). Hydroxypropyl β-CDs and γ-CD were obtained from ASTEC (Whippany, NJ, USA). α-tetralone, (*S*)-(+)-1-indanol, (*R*)-(−)-1-indanol, (*S*)-(+)-1-tetralenol, (*R*)-(−)-1-tetralenol, 1-benzosuberone, 2-methyl-1-tetralone, 1-methyl-2-tetralone, 4-methyl-1-tetralone, 1-methyl-3-indanone, 4-hydroxy-α-indanone, 5-hydroxy-α-indanone, 6-methoxy-α-indanone, 1,5-dihydroxytetralin, 5,7-dimethyl-α-tetralone, 7-methoxy-α-tetralone, 1-carboxy-3-indanone, 1-aminoindan, 1-aminotetralin, methylmagnesium bromide were obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI, USA). Sodium borohydride was obtained from Sigma Chemical Co. (St. Louis, MO, USA). Platinum oxide was obtained from Engelhard Chemical Co. (Newark, NJ, USA).

2.2. Methods

A Waters Quanta 4000 CE system was used. The length of the capillary to the detector was 52.4 cm and was 60 cm end-to-end. The inner diameter of the capillary was 75 μm and UV detection was performed at 214 nm. The buffer was prepared using NaH_2PO_4 and Na_2HPO_4. All samples were dissolved in methanol. The samples were hydrostatically (2 s) introduced into the cathodic or anodic end of the capillary in the reversed or conventional electrophoretic polarity mode, respectively. The analysis was carried out at 21±2°C. A voltage of −20 kV or −15 kV was used for the reversed electrophoretic polarity mode. A voltage of 10 kV was used for the conventional electrophoretic polarity mode. Note that the electroosmotic flow cannot be measured in the reversed polarity mode.

2.3. Synthesis of tetraline, indan and benzosubern derivatives

Detailed synthesis and characterization of the various derivatives of tetralin, indan and benzosuberan were previously reported [23]. In brief all primary alcohol derivatives were prepared by mixing the appropriate ketones with sodium borohydride in methanol. After quenching the reaction by adding water to the mixture, the product was extracted with hexane and dried over anhydrous magnesium sulfate. After evaporation of hexane, the product was dissolved in methanol to be introduced to the capillary electrophoretic system. All tertiary alcohols were synthesized by mixing the appropriate ketones with

methymagnesium bromide in the presence of tertiary butylether. After stirring the mixture for 8 h, water was added to quench the reaction. Again, the product was extracted with hexane and dried over anhydrous magnesium sulfate. Alkyl derivatives (1-methyltetralin, 1-methylindan and 1-methylbenzosuberan) were synthesized by dehydration of the appropriate tertiary alcohols followed by hydrogenation catalyzed with platinum oxide.

3. Results and discussion

The electrophoretic data for the enantio-resolution of twenty-four racemic indans, tetralins and benzosuberans using several different CD mixtures are listed in Table 1 along with their chemical structures. The compounds consist of fifteen hydroxy, two carboxy, two amino, two ketone and three methyl derivatives of tetralin, indan and benzosuberan. Six of these compounds have two stereogenic centers. All four stereoisomers were resolved except in the case of 1-carboxy-3-indanol where only one of the two possible enantiomeric pairs was observed.

An electropherogram showing the enantiomeric separation of 1-indanol, 1-hydroxytetralin and 1-hydroxybenzosuberan is shown in Fig. 1. Hydroxybenzosuberan binds most strongly to sulfated β-CDs followed by 1-hydroxytetralin and 1-indanol. The shorter migration time of a neutral analyte in the reversed electrophoretic polarity mode indicates a stronger interaction with sulfated CDs [28]. The slowest migrating 1-indanol was the best resolved of the three compounds. This indicated that stronger binding does not always result in better resolution [29]. The larger benzosuberan binds more strongly to the sulfated β-CDs but was poorer enantioselective interactions than the smaller 1-indanol. The enantioresolution obtained for these compounds by capillary electrophoresis is opposite to that obtained by gas chromatography using Chiraldex B-PH columns [23]. In GC, the enantioresolution of 1-hydroxybenzosuberan exceeded that of the smaller ring homologues. The capillary electrophoretic resolution of 1-hydroxybenzosuberan can be enhanced by the addition of γ-CD to the running buffer which contains sulfated β-CDs. Fig. 2 shows the enhanced enantioseparation for 1-hydroxybenzosuberan and 1-methylbenzosuberan.

The enantioresolution of 1-methylindan, 1-methyltetralin and 1-methylbenzosuberan was investigated by changing the concentration of sulfated β-CDs (Fig. 3a and b) or by adding γ-CD to the running buffer containing sulfated β-CDs (Fig. 3c and d). As in the case of hydroxyl derivatives, methyl derivatives of indan and tetralin were resolved with sulfated β-CDs, but there was no enantioresolution of 1-methylbenzosuberan under these experimental conditions (Fig. 3a). As deduced from the migration order, the relative binding strength of the alkyl derivatives toward sulfated β-CDs is 1-methylbenzosuberan followed by 1-methyltetralin and 1-methylindan, which is consistent with those obtained in the case of hydroxyl derivatives. In both cases, it can be deduced that (a) the ring size of these homologues determines the binding strength, and (b) hydrophobic interaction seems to be the main driving force for complexation. The increase in concentration of sulfated β-CDs does not seem to significantly alter the resolution of the individual components (Fig. 3b). However, the addition of γ-CD to the running electrolyte, in addition to the sulfated β-CDs, results in a greater than baseline resolution of 1-methylbenzosuberan, as well as better resolution of 1-methyltetralin and 1-methylindan. Increasing the concentration of γ-CD up to 21.2 m*M* resulted in consistently longer migration times and better resolutions. In the case of 21.2 m*M* γ-CD, 1-methylindan migrates first while 1-methylbenzosubran last. The reversal of the migration order suggests that 1-methylbenzosubran binds most strongly with both sulfated β-CDs and γ-CD.

The near UV transparency and high water solubility of electrically neutral γ-CD makes optimization of these enantioseparations a simple, straightforward process. Addition of γ-CD does not increase the UV background or the current of the run buffer. One can simply add more CD until enantioresolution is achieved.

Another successful dual CD system was obtained by combining sulfated β-CDs and hydroxypropyl β-CDs. Electropherogams of the enantioseparation of 1-hydroxy-2-methyltetralin and 2-hydroxy-1-methyltetralin are shown in Fig. 4. Because both of these compounds have two stereogenic centers, there

Table 1
Electrophoretic data for the chiral separations of tetralins, indans, and benzosuberans

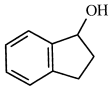
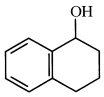
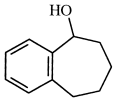
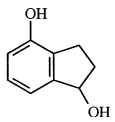
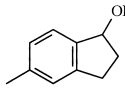
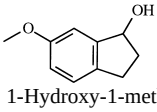
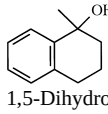
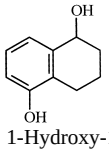
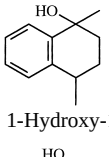
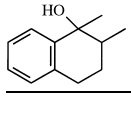
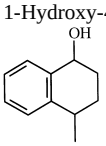
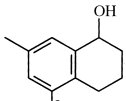
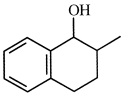
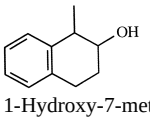
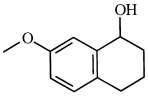
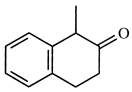
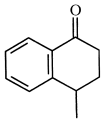
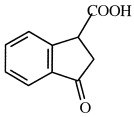
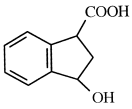
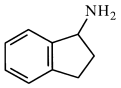
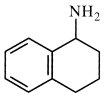
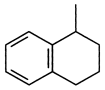
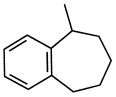
Compound	t_1(min)[a]	t_2(min)[b]	R_s	Electrophoretic condition[c]
Alcohols				
1-Indanol 	32.7 (*S*)-(+)	33.9 (*R*)-(−)	2.22	A
1-Hydroxytetralin 	25.5 (*S*)-(+)	26.1 (*R*)-(−)	1.11	A
1-Hydroxybenzosuberan 	28.9	29.6	1.33	B
1,4-Dihydroxyindan 	30.2	33.7	5.27	A
1-Hydroxy-5-methylindan 	26.6	27.3	1.25	A
1-Hydroxy-6-methoxyindan 	24.8	25.9	2.10	A
1-Hydroxy-1-methyltetralin 	23.2	25.3	4.47	C
1,5-Dihydroxytetralin 	19.2	20.7	3.81	A
1-Hydroxy-1,4-dimethyltetralin 	14.2/15.3[d]	14.9/16.2[d]	2.93/3.52[d]	D
1-Hydroxy-1,2-dimethyltetralin 	11.5/12.2[d]	12.2/13.1	1.66/1.75	D

Table 1. Continued

Compound	t_1(min)[a]	t_2(min)[b]	R_s	Electrophoretic condition[c]
1-Hydroxy-4-methyltetralin 	20.8/22.9[d]	22.1/23.6	2.76/1.40	A
1-Hydroxy-5,7-dimethyltetralin 	43.5	44.9	1.53	A
1-Hydroxy-2-methyltetralin 	25.1/27.4[d]	25.9/27.9	1.31/0.88	E
2-Hydroxy-1-methyltetralin 	10.5/11.3[d]	10.8/12.2	1.8/3.5	D
1-Hydroxy-7-methoxytetralin 	20.7	21.7	2.1	A
Ketones				
1-Methyl-2-tetralone 	12.1	12.4	1.20	D
4-Methyl-1-tetralone 	12.3	12.6	1.2	D
Acids				
1-Carboxy-3-indanone 	15.1	15.4	1.20	D
1-Carboxy-3-indanol 	19.8[e]	20.5	1.50	D

(Cont.)

Table 1. Continued

Compound	t_1(min)[a]	t_2(min)[b]	R_s	Electrophoretic condition[c]
Amines				
1-Aminoindan	8.5	8.8	2.65	F
				
1-Aminotetralin	8.8	9.0	2.05	F
				
Hydrocarbons				
1-Methylindan	26.9	28.5	2.84	G
				
1-Methyltetralin	31.6	34.1	3.57	G
				
1-Methlybenzosuberan	32.3	34.1	2.45	G
				

[a] Migration time (in minutes) of the first eluting enantiomer.
[b] Migration time (in minutes) of the second eluting enantiomer.
[c] Electrophoretic conditions:
A: 6.5 m*M* S-β-CDs, V=−15 kV, 40 m*M* phosphate buffer (pH 4.1),
B: 6.5 m*M* S-β-CDs, 5.8 m*M* γ-CD, V=−15 kV, 20 m*M* phosphate buffer (pH 3.9),
C: 6.5 m*M* S-β-CDs, V=−15 kV, 40 m*M* phosphate buffer (pH 3.1),
D: 6.5 m*M* S-β-CDs, V=−20 kV, 10 m*M* phosphate buffer (pH 3.3),
E: 6.5 m*M* S-β-CDs, 19.2 m*M* HB-β-CD, V=−20 kV, 10 m*M* phosphate buffer (pH 3.9),
F: 2.3 m*M* S-β-CDs, V=10 kV, 10 m*M* phosphate buffer (pH 7.0),
G: 6.5 m*M* S-β-CDs, 21.1 m*M* γ-CD, V=−15 kV, 20 m*M* phosphate buffer (pH 4.5).
[d] Two pairs of enantiomers.
[e] Only one of the two possible enantiomeric pairs were observed.

are four stereoiosmers. In the case of 2-hydroxy-1-methyltetralin, four peaks are readily observed using only sulfated β-CDs as chiral additives to the running electrolyte. However, in the case of 1-hydroxyl-2-methyltetralin, two peaks were observed corresponding to the diastereomers (data not shown). By adding 19.2 m*M* hydroxpropyl β-CDs to the running electrolyte containing 6.5 m*M* sulfated β-CDs, the resolution of all four stereoisomers became possible.

In addition to the neutral indan, tetralin and benzosuberan derivatives, some charged analogues were enantio-resolved as well. In the case of 1-carboxy-3-indanone, baseline resolution was observed in the reversed electrophoretic polarity mode using sulfated β-CDs as chiral additives to the

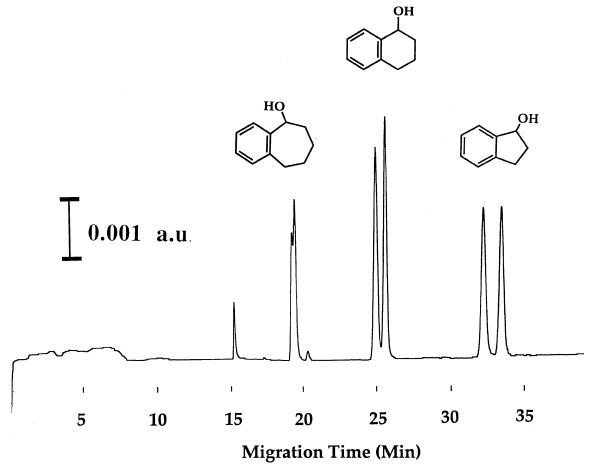


Fig. 1. Electropherogram of the separation of 1-hydroxybenzosuberan, 1-hydroxytetralin, and 1-indanol. The electrolyte consisted of 6.5 m*M* sulfated β-CDs in 40 m*M* phosphate buffer (pH 4.1).

running electrolyte (see Table 1). However, in the case of 1-carboxy-3-indanol, separation of only one of the two possible enantiomeric pairs was observed. Cationic 1-aminoindan and 1-aminotetralin could not be detected in the reversed electrophoretic mode using sulfated β-CDs as chiral additives. The enantioresolution of these two compounds was attempted using sulfated β-CDs in the conventional electrophoretic polarity mode. The successful resolution of both compounds was obtained using 3.3 m*M* sulfated β-CDs in 10 m*M* phosphate buffer (pH 7.0) as shown in Fig. 5.

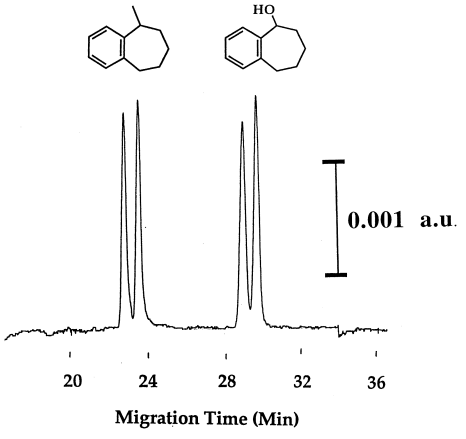


Fig. 2. Electropherogram of the separation of 1-methylbenzosuberan and 1-hydroxybenzosuberan. The electrolyte consisted of 6.5 m*M* sulfated β-CDs and 5.8 m*M* γ-CD in 20 m*M* phosphate buffer (pH 3.9).

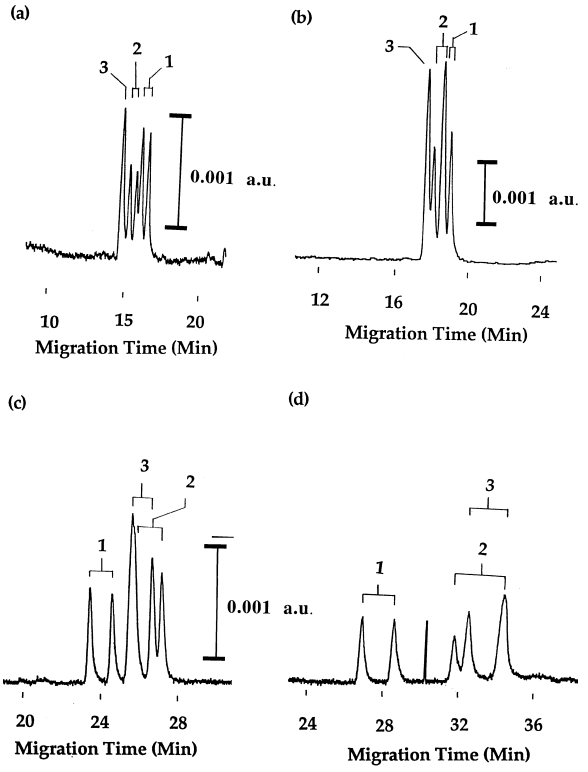


Fig. 3. Electropherograms of the separation of 1-methylindan (1), 1-methyltetralin (2) and 1-methylbenzosuberan (3). The electrolyte consisted of (a) 3.3 m*M* sulfated β-CDs (pH 3.3), (b) 6.5 m*M* sulfated β-CDs (pH 4.5), (c) 5 m*M* sulfated β-CDs and 5.8 m*M* γ-CD (pH 4.5) and (d) 6.5 m*M* sulfated β-CDs and 21.2 m*M* γ-CD (pH 4.5).

4. Conclusion

The successful use of mixtures of sulfated β-CDs and neutral native γ-CD or hydroxypropyl β-CDs as chiral additives in capillary electrophoresis was reported for the enantioseparation of the neutral and anionic derivatives of indan, tetralin and ben-

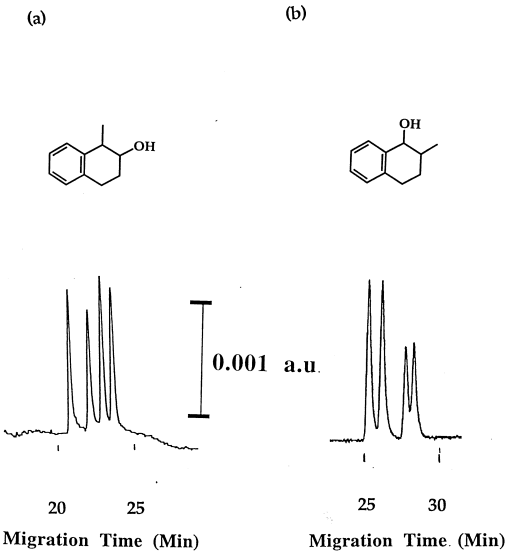


Fig. 4. (a) Electropherogram of the separation of 2-hydroxy-1-methyltetralin. The electrolyte consisted of 6.5 m*M* sulfated β-CDs in 10 m*M* phosphate buffer (pH 3.3). (b) Electropherogram of the separation of 1-hydroxy-2-methyltetralin. The electrolyte consisted of 6.5 m*M* sulfated β-CDs and 19.2 m*M* hydroxypropyl β-CDs in 10 m*M* phosphate buffer (pH 3.9).

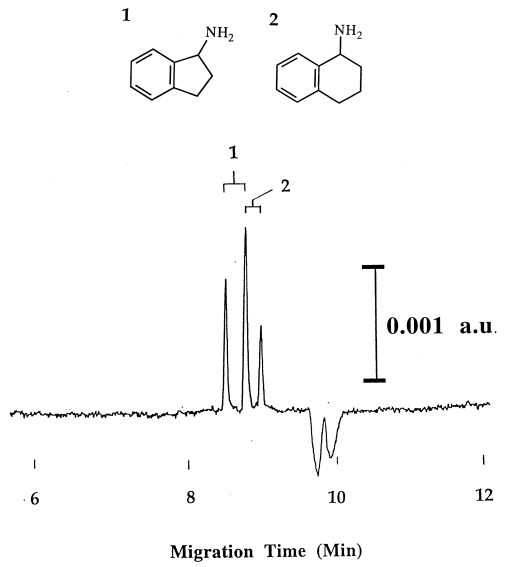


Fig. 5. Electropherogram of the separation of 1-aminoindan and 1-aminotetralin. The electrolyte consisted of 3.3 m*M* sulfated β-CDs in 10 m*M* phosphate buffer (pH 7.0), *V*=10 kV.

zosuberan in the reversed electrophoretic polarity mode. The addition of neutral CD additives to the run buffer frequently enhanced the enantioresolution of these neutral compounds as compared to solutions containing only anionic sulfated β-CDs. Cationic 1-aminoindan and 1-aminotetralin were enantioresolved in the conventional electrophoretic mode using only sulfated β-CDs as chiral additives. The UV transparency together with the high water solubility of γ-CD and hydroxypropyl β-CDs, facilitates the optimization task for the enantioseparations of the analytes in this study.

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