Separation of enantiomers of selected chiral sulfoxides with cellulose tris(4-chloro-3-methylphenylcarbamate)-based chiral columns in high-performance liquid chromatography with very high separation factor

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Abstract

The present study reports successful separations of enantiomers of selected chiral sulfoxides with very high separation factor in high-performance liquid chromatography by using chiral columns prepared with the chiral selector cellulose tris(4-chloro-3-methylphenylcarbamate). High separation factors were observed in polar organic, as well as in hydrocarbon-alcohol-type mobile phases. The key structural components of the solute for obtaining high chiral recognition are discussed as well as thermodynamic quantities of analyte adsorption on the chiral stationary phase were determined. Experiment aimed at the enantioselective extraction of racemates from solution are also described.

Keywords:

Separation of enantiomers; Polysaccharide-based chiral stationary phases; Enantioselective extraction; Thermodynamic quantities of adsorption.

1. Introduction

Polysaccharide phenylcarbamates are recognized as one of the most powerful group of chiral selectors for the liquid-phase separation of enantiomers on analytical, preparative and even on production-scale [1-3]. The application of polysaccharide-based chiral selectors together with classical high-performance liquid chromatography [1, 2], is also described for the separation of enantiomers in batch low-pressure liquid chromatography [4], recycling mode [5], in different variations of simulated moving bed chromatography [6, 7], supercritical fluid chromatography [8-10], nano-liquid chromatography [11-14] and capillary electrochromatography [11-13, 15, 16]. Despite the widespread application of polysaccharide-based chiral selectors their chiral recognition mechanism is currently not well understood. A lot of effort went over the years into getting more understanding of the underlying mechanisms of enantiomer discrimination with polysaccharide phenylcarbamates by using various experimental, statistical, screening and modelling approaches [17-20], but some major questions still remain unanswered. One of the very early assumptions made by Okamoto and co-workers regarding the key role played by carbamate moieties in chiral recognition with polysaccharide phenylcarbamates has been proven correct and remains undoubtedly valid after more than 3 decades [21]. By considering the carbamate moiety as a key interaction site for chiral analytes and also the effect of electron-donating and electron-withdrawing substituents on the phenyl moiety on the electron density on the carbamate moieties, one of the authors of the current study proposed an effective set of polysaccharide-based chiral selectors about two decades ago which were later commercialized by several companies and are in widespread use today [1, 22-24]. In order to gain deeper insight in

enantioselective recognition mechanisms involving polysaccharide phenylcarbamates more cases of exceptional behavior of these materials, such as unusually high enantioselectivity, effect of mobile phase modifiers and temperature on elution order of enantiomers, etc. need be carefully studied in hope that these extraordinary effects may provide clues regarding the most critical structural characteristics of analytes and selectors, as well as about the forces involved in enantioselective selector-selectand binding.

Chiral sulfoxides have been identified in a variety of natural products and their synthetic derivatives. Synthetic chiral sulfoxides are widely used as valuable drug compounds (e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole) [25, 26], as pesticides (fipronil, propargit, methiocarb sulfoxide, fensulfothion, etc.) [26], chiral auxiliaries and chiral ligands to metals [27, 28]. The synthesis of enantiomerically enriched or pure sulfoxides is currently of primary interest [29-31]. The enantioselective biological activity of chiral sulfoxides is well documented and became the reason for developing some of them as enantiomerically pure chiral drugs [25]. For instance, together with racemic omeprazole, its enantiomerically pure analogue, S-omeprazole is used in clinical practice and some other analogues are also under development [9, 25]. Chromatographic methods have been used for the separation of enantiomers of chiral sulfoxides for more than 20 years [32-41] and together with analytical- [32-38, 40, 41], their preparative potential has been proven [38, 39]. Polysaccharide-based chiral columns are well suited for the separation of enantiomers of chiral sulfoxides [32, 33, 36, 37, 39-41].

In our earlier study, high separation factors exceeding 100 were reported for one of the non-commercial chiral sulfoxidex with cellulose tris(3,5-dichlorophenylcarbamate) as a chiral selector and 2-propanol as a mobile phase [37]. More detailed studies on this group of analytes was impossible because they were not commercially available. In the frame of our on-going project the chiral sulfoxide reported in ref. 37 and many analogues of it were synthesized in order to investigate the effect of structural features of analyte on its enantioselective recognition by polysaccharide phenylcarbamates. This paper reports part of our results in this direction together with the effects of mobile phase composition and temperature on separation of enantiomers.

2. Experimental part

2.1 Materials

2-Mercaptobenzoic acid, benzyl bromide, amines (R-NH2), dioxane, triethylamine(Et3 N), trifluoroacetic acid (TFA), N,N-dimethylformamide (DMF), (benzotriazol-1-yloxy)tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), 3-chloroperoxybenzoic acid (MCPBA), chloroform and anisole required for synthesis of chiral sulfoxides used in this study (Fig. 1) were acquired from Sigma-Aldrich (Milan, Italy). Chiral sulfoxides were synthesized based on general scheme shown in Fig. 2 and previously described in ref. [31]. The reaction of commercially available 2-mercaptobenzoic acid (1) with benzyl bromide was promoted by triethylamine in dioxane to form the corresponding sulfide derivative (2). Next, the carboxylic acid functionally was transformed in the corresponding amide (3) by coupling with methylamine, dimethylamine and 4-methoxybenzylamine. Finally, oxidation of the sulfide group with

MCPBA in chloroform at 0℃ led to the formation of the sulfoxides (4), 2-(benzylsulfinyl)-N-methylbenzamide and 2-(benzylsulfinyl)-N,N-dimethylbenzamide, which were purified by flash chromatography on silica gel (silica gel 60, 60-200 μm, Merck, Darmstadt, Germany). The primary benzamide derivative (7), was obtained by deprotection of the corresponding 4-methoxybenzylamide (5) followed by oxidation with MCPBA (Fig. 2).

Chromatographic grade acetonitrile, n-hexane, methanol and 2-propanol used as mobile phase components were acquired from Carl Roth (Karlsruhe, Germany). Commercially available chiral columns (4.6 x 250 mm, 5 μm particle size) Lux Cellulose-1 (Cellulose tris(3,5-dimethylpnenylcarbamate coated onto silica) , Lux Cellulose-3 (Cellulose tris(4-methybenzoate coated onto silica) and Lux Cellulose-4 (Cellulose tris(4-chloro-3-methylpnenylcarbamate coated onto silica) were provided by Phenomenex Inc. (Torrance, CA, USA). Other chiral columns used in this study were laboratory-made by coating appropriate amounts of chiral selector on aminopropylsilanized fully porous silica particles of 5 micrometer nominal particle size and 100 nm nominal pore size or alternatively on superficially porous silica particles with 3.6 micrometer nominal particle size and 20 nm nominal pore size. Silica particles were provided by Phenomenex Inc. Cellulose tris(4-chloro-3-methylpnenylcarbamate was synthesized as described in ref. [22].

2.2. Instruments

All HPLC experiments were performed with an Agilent 1200HPLC instrument (Agilent Technologies, Waldbronn, Germany) equipped with a G1367C HiP ALS-SL autosampler, G1316 B TCC-SL temperature controller, G1311A quaternary pump and

G1314DVWD variable wavelength detector. The Chemstation software (version B.03.02-SR2) was used for instrument control, data acquisition and data processing. HPLC separations were performed at 20°C at 1 ml/min mobile phase flow rate if not indicated otherwise. UV-detection was performed at 240 nm. The optical rotation sign of resolved enantiomers of 2-(benzylsulfinyl)-benzamide was assigned based on ref. 37 in which a circular dichroism and polarimetric detectors were sequentially connected to a UV-detector.

2.3 Enantioselective adsorption

Enantioselective adsorption experiments were performed in a thermostated cell having a volume of 100 ml. The cell was immersed in a water bath and temperature was set at 20°C. Mixing was provided by magnetic stir bar. Two mg of racemic 2-(benzylsulfinyl) benzamide and 1 mg of 1,3,5-tri-tertiary-butylbenzene were dissolved in 50 ml n-hexane/2-propanol mixture (70/70, v/v), 10 ml of this solution was diluted with 40 ml of n-hexane/2-propanol mixture (70/70, v/v) and placed in the thermostated adsorption cell. Before addition of adsorbent the sample was taken and analyzed for its enantiomeric composition. Afterwards a weighted amount of adsorbent was added under continuous stirring and samples of supernatant were taken at certain time intervals, immediately filtered through 0.45μm polypropylene filter and analyzed for enantiomer composition by HPLC.

3. Results and Discussion

3.1 Effect of structure of chiral analyte and mobile phase composition on separation selectivity

Enantioseparation of five chiral sulfoxides shown in Fig. 1 was studied in acetonitrile, methanol, 2-propanol, n-hexane/2-propanol and acetonitrile-water mobile phases in order to evaluate the importance of free amide group and its distance from benzylsulfinyl moiety for chiral recognition. As it can be seen from the results shown in Fig. 3, the free amide group plays an important role for selective recognition of enantiomers since its methylation and demethylation both reduce the selectivity of recognition in all mobile phases studied. This effect was reported on the international scientific conferences over the years, as well as the present manuscript was ready for submission when similar result based on our earlier published studies [36, 37,] but with another chiral selector was reported by Cirilli and co-workers [38]. The most striking effect of a structural detail on enantioselective recognition is the major loss in selectivity caused by shifting the benzylsulfinyl moiety from ortho- to meta-position in relation to the amide moiety (Fig. 3). It is interesting to note that the observed effect does not depend significantly on the mobile phase used and the pattern is the same in all studied mobile phases (Table 1). Thus, based on the critical role played by the position of this particular moiety on enantioselectivity, the spatial distance between various structural details part of analyte molecules and interaction sites on the chiral selector becomes of great significance. The exact type of interaction taking place between analyte and chiral selector (CS) becomes evident as we consider the significantly higher enantioselectivity observed for all enantioseparated sulfoxides (shown only for 2-(benzylsulfinyl)-N,N-dimethylbenzamide in Fig. 4) in acetonitrile (aprotic solvent) compared to methanol

(protic solvent), as well as the significant decrease in enantioselectivity in aqueous acetonitrile compared to acetonitrile (Fig. 4 and Table 1). All these results support our earlier idea [36,37] that that hydrogen bonding plays an important role in the chiral recognition of studied analytes with cellulose tris(phenylcarbamate)s.

The chiral column based on cellulose tris(3,5-dichlorophenylcarbamate) used in our earlier study that provided the highest separation factor of enantiomers ever reported in HPLC by that time [37] is not stable in n-hexane/2-propanol mixture of any composition. Therefore, the use of n-hexane in mixture with 2-propanol with the purpose of increasing enantiomer retention in the hope of improving the separation factor was not possible. In contrast to cellulose tris(3,5-dichlorophenylcarbamate), cellulose tris(4-chloro-3-methylphenylcarbamate) is insoluble in n-hexane/2-propanol mixtures of any composition. This provides the opportunity for further adjusting retention and selectivity based on the composition of the mobile phase. With increasing the content of n-hexane in the mobile phase, retention of both enantiomers increased significantly for all studied sulfoxides. Increase in separation selectivity was also observed with increasing n-hexane content up to 80% (v/v) (Fig. 5). Further increasing the n-hexane content in the mobile phase did not produce a clear trend and this region of MP composition requires further studies. It must be emphasized that enantioselectivity was spectacular with 250x4.6 size Lux Cellulose-4 column under normal phase conditions, reaching values ~~of several~~ over 700 ~~hundreds~~. At the same time, the analysis time was several days and exact measurement of the retention time of the second enantiomer was almost impossible. Therefore, either very short columns must be used or the selectivity needs to be measured in some other mode than elution (e.g. in displacement mode).

3.2 Fast separation of enantiomers

Exceptionally high enantioselectivity of cellulose tris(4-chloro-3-methylphenylcarbamate) towards some of studied chiral sulfoxides offered the possibility to perform fast separations by reducing the content of chiral selector of the chiral stationary phase (CSP), the column length and/or increasing the mobile phase flow rate. This strategy was evaluated with more or less success and baseline separations of enantiomers were observed with sub-minute analysis times. In reality, shortening the analysis time by lowering the content of chiral selector of the CSP can be ineffective in cases where selectivity is very large because retention factors/times of the second enantiomer can still be too long. Therefore, in addition to 2-(benzylsulfinyl)-benzamide (with highest selectivity of separation) separation of enantiomers of 2-(benzylsulfinyl)-N-methylbenzamide and 2-(benzylsulfinyl)-N,N-dimethylbenzamide were also studied and baseline separation of enantiomers were obtained with the analysis time below 1 minute. The content of chiral selector in the CSP was lowered to 5% (w/w) from 20% or higher with commercially available columns for the separation example shown in Fig. 6a; at the same time, column length was reduced to 30mm with the same purpose. Baseline separation of enantiomers was still achieved even at a flow rate as high as 5 ml/min, within 25 seconds. Since the used instrument did not allow for higher flow rates further shortening of analysis times from 25 down to 10 seconds was achieved by further reducing the content of chiral selector from 5 to 2% (w/w) (Fig. 6b). Further reduction of analysis time was managed on the same HPLC instrument by using a column with the internal diameter 2.1 mm which requires lower flow rates well below the maximum limit

of the instrument . This enabled a shortening of analysis time down to 6 seconds (Fig. 6c). Few examples of baseline HPLC separation of enantiomers on the scale of seconds have been published earlier and also in more recent literature [42-46].

3.3 Effect of temperature on retention and separation selectivity

Temperature dependence of analyte retention and separation selectivity was studied in order to shed some light on the separation mechanism. The differential enthalpy and entropy of separation were calculated in all mobile phases studied based on equation 1:

$$\ln \alpha = -\frac{\Delta_{j,i}\Delta H^0}{RT} + \frac{\Delta_{j,i}\Delta S^0}{R} \qquad (1)$$

where α is the separation factor, $\Delta_{j,i}\Delta H°$ and $\Delta_{j,i}\Delta S°$ are the enthalpy and entropy differences related to the adsorption of both enantiomers, respectively, T is absolute temperature and R is the gas constant. As an example, the linear relationship observed between $\ln\alpha$ and 1/T is shown in Fig. 7 for the separation of 2-(benzylsulfinyl) benzamide in acetonitrile mobile phase. This dependence was constructed based on experimental results shown in Table 2.

The thermodynamic quantities $\Delta\Delta H°$ and $\Delta\Delta S°$ are summarized in Table 3 along with the estimated enantiomer co-elution temperature. Some interesting conclusions can be drawn from the data shown in Table 3. In particular, for 2-(benzylsulfinyl)-benzamide, the enantiomers of which are best separated in all studied mobile phases, the enthalpy favors enantioseparation in all mobile phases while entropy disfavors it in acetonitrile and favors it in all pure alcohol or alcohol-based mobile phases. This result is different from the observation made in ref. 38 where the authors report enthalpic control of separation of

enantiomers of the same compound on covalently immobilized cellulose(3,5-dichlorophenylcarbamate)-based chiral column in ethanol as a mobile phase.

In addition, the entropy contribution increases from methanol to 2-propanol and decreases with increasing amount of n-hexane in 2-propanol/n-hexane mobile phases. For all other studied compounds except the above mentioned 2-(benzylsulfinyl)-benzamide the enthalpy favors and the entropy disfavors separation of enantiomers in all studied mobile phases (Table 3). In addition, calculations predict a reversal of enantiomer elution order for 3-benzylsulfinyl-N-methylbenzamide in acetonitrile at around 37°C. This was not observed experimentally but the peaks which were baseline resolved at 5°C co-eluted at 40°C and no reversal of enantiomer elution order was observed by further increase of separation temperature to 60°C.

It must be mentioned that equation (1) must be used with certain care for above mentioned calculations. In particular, this equation is only valid under the assumption that no change takes place in the morphology of either the chiral selector or the selectand (analyte) in the temperature range studied. Our recent thermoanalytical studies on polysaccharide phenylcarbamates suggests that these materials undergo some transition that starts at temperatures near 30°C (data not shown).

3.4 Enantioselective adsorption

The chromatographic separation process is understood to involve successive single adsorption and desorption steps, separated by distance increments along the column, resulting in a cumulative process generically referred to as retention. Given the multitude of adsorption and desorption steps taking place along the column, any bias

toward one specific species can be sufficient to achieve baseline separation between enantiomers. However, whenever this bias is significant enough to result in very large selectivity (as was observed in the present study), perhaps a process involving one single adsorption step may be sufficient to selectively extract one of the enantiomers from solution (like in a batch process).

In this preliminary study a CSP containing 25% (w/w) of cellulose tris(4-chloro-3-methylphenylcarbamate), as well as crude cellulose tris(4-chloro-3-methylphenylcarbamate) polymer were used as adsorbents for the selective extraction of one enantiomer from the solution of racemate. Various amounts of CSP and crude polymer were used, as well as various solvents. The results of one of these experiments are shown in Fig. 8. Interestingly, the process of selective extraction from solution is very fast: the filtrate contained primarily the first enantiomer even after only 5 seconds of contact with the adsorbent (Figs. 8 and 9). After 5 minutes of equilibration, only trace amounts of the second enantiomer were detectable in the filtrate. This preliminary experiment shows that chiral selectors may act as highly specific extractants in very efficient and inexpensive processes for the large scale separation of enantiomers.

4. Conclusions

The present study illustrates the drastic effect of analyte structural details on their chiral recognition ability by polysaccharide-based chiral selectors. Interestingly, the structure-enantioselectivity pattern was quite similar in various mobile phases. Studies of separations at different temperature enabled to calculate thermodynamic quantities of

separation process. In acetonitrile as the mobile phase, the enthalpic term favored separation of enantiomers at the room temperature while in methanol and 2-propanol containing mobile phases the contribution of entropy was dominant. High enantioselectivity of recognition of cellulose tris(4-chloro-3-methylphenylcarbamate) made possible fast baseline separation of enantiomers with high efficiency as well as efficient resolution of enantiomers based on enantioselective adsorption from solution.

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Legends to figures:

Fig. 1 Structure of studied chiral sulfoxides.

Fig. 2 Schema of synthesis of sulfoxides.

Fig. 3 Separation of enantiomers of 2-(benzylsulfinyl)-benzamide (a), 2-(benzylsulfinyl)-N-methylbenzamide (b), 2-(benzylsulfinyl)-N,N-dimethylbenzamide (c) and 3-(benzylsulfinyl)-benzamide (d) on chiral column (4.6 x 30 mm) packed with 5 μm aminopropylsilanized silica coated with 20% cellulose tris(4-chloro-3-methylphenylcarbamate) (w/w). Mobile phase was acetonitrile with the flow rate 2 ml/min.

Fig. 4 Separation of enantiomers of 2-(benzylsulfinyl)-N,N-dimethylbenzamide using a) acetonitrile, b) methanol and c) acetonitrile/water 95/5 (v/v) as mobile phases. Chiral column (4.6 x 30 mm) was packed with 5 μm aminopropylsilanized silica coated with 20% cellulose tris(4-chloro-3-methylphenylcarbamate) (w/w). Other conditions were as indicated in the legend to Fig. 3.

Fig. 5 Dependence of the retention factor for the second enantiomer and the separation factor of 2-(benzylsulfinyl)-benzamide enantiomers on the content of n-hexane in 2-propanol. Chiral column (4.6 x 30 mm) was packed with 5 μm aminopropylsilanized silica coated with 20% cellulose tris(4-chloro-3-methylphenylcarbamate) (w/w).

Fig. 6 Fast separation of enantiomers of 2-(benzylsulfinyl)-N,N-dimethylbenzamide on chiral column packed with superficially porous silica particles containing 5% (a) and (c) and 2% (b) cellulose tris(4-chloro-3-methylphenylcarbamate) (w/w). The

column size was 4.6 x 30 mm in case (a) and (b) and 2.1 x 50 mm in case (c). Flow rate of the mobile phase was 5 ml/min and separation temperature 20°C.

Fig. 7 Example of linear graphs used for calculation of thermodynamic quantities. The analyte was 2-(benzylsulfinyl)-benzamide. Chiral column in all thermodynamic calculations was of 4.6 x 30 mm size packed with 5 μm aminopropylsilica coated with 20% cellulose tris(4-chloro-3-methylphenylcarbamate) (w/w). Mobile phase in this example was ACN with the flow rate 2 ml/min.

Fig. 8 Time dependence of fraction of each enantiomers of 2-(benzylsulfinyl)-benzamide in solution. In this particular experiment 1 mg of racemic 2-(benzylsulfinyl)-benzamide was dissolved in 50ml n-hexane/2-propanol (70/30, v/v) and 0.3 g of cellulose tris(4-chloro-3-methylphenylcarbamate) was used as the adsorbent. The samples were analyzed using Lux Cellulose-3 chiral column and n-hexane/2-propanol (70/30, v/v) as the mobile phase with the flow rate 2 ml/min. The column was thermostated at 25°C. UV detector was set at 240 nm.

Fig. 9 Results of enantioselective adsorption from the solution of racemate. Chromatogram of the starting solution containing internal standard before addition of the adsorbent (a), chromatogram of the filtrate 5 seconds (b) and 5 minutes (c) after addition of 0.3g of cellulose tris(4-chloro-3-methylphenylcarbamate). ~~) (b) and chromatogram of the same solution 5 minutes after addition of the adsorbent (c~~). HPLC conditions were as indicated in the legend to Fig. 8.

Figure 1

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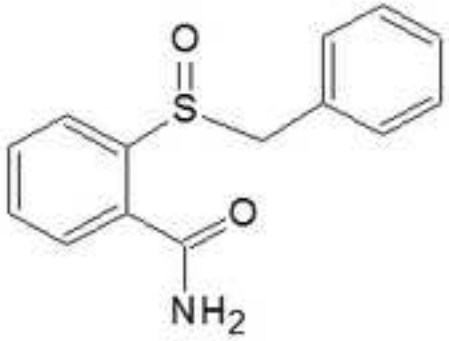
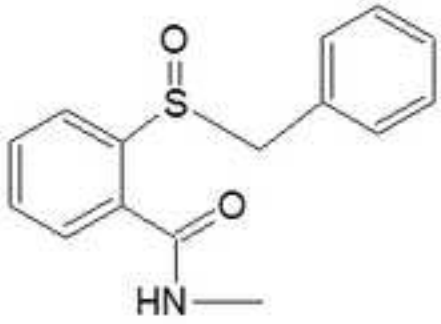
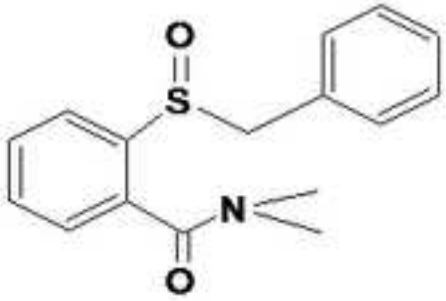
2-(Benzylsulfinyl)-benzamide



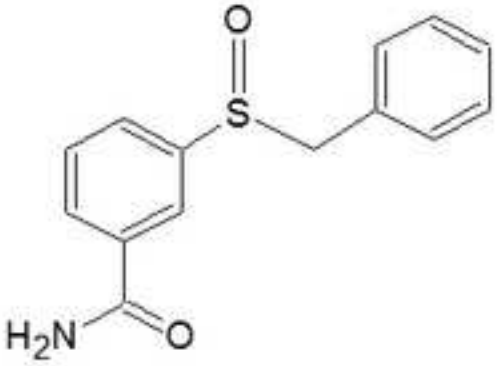
2-(Benzylsulfinyl)-N-methylbenzamide



2-(Benzylsulfinyl)-N,N-dimethylbenzamide



3-(Benzylsulfinyl)-benzamide



3-(Benzylsulfinyl)-N-methylbenzamide

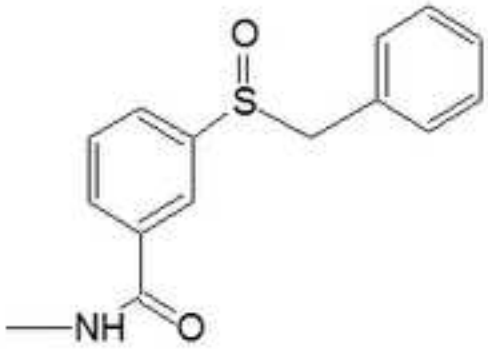


Fig. 1

Figure 2

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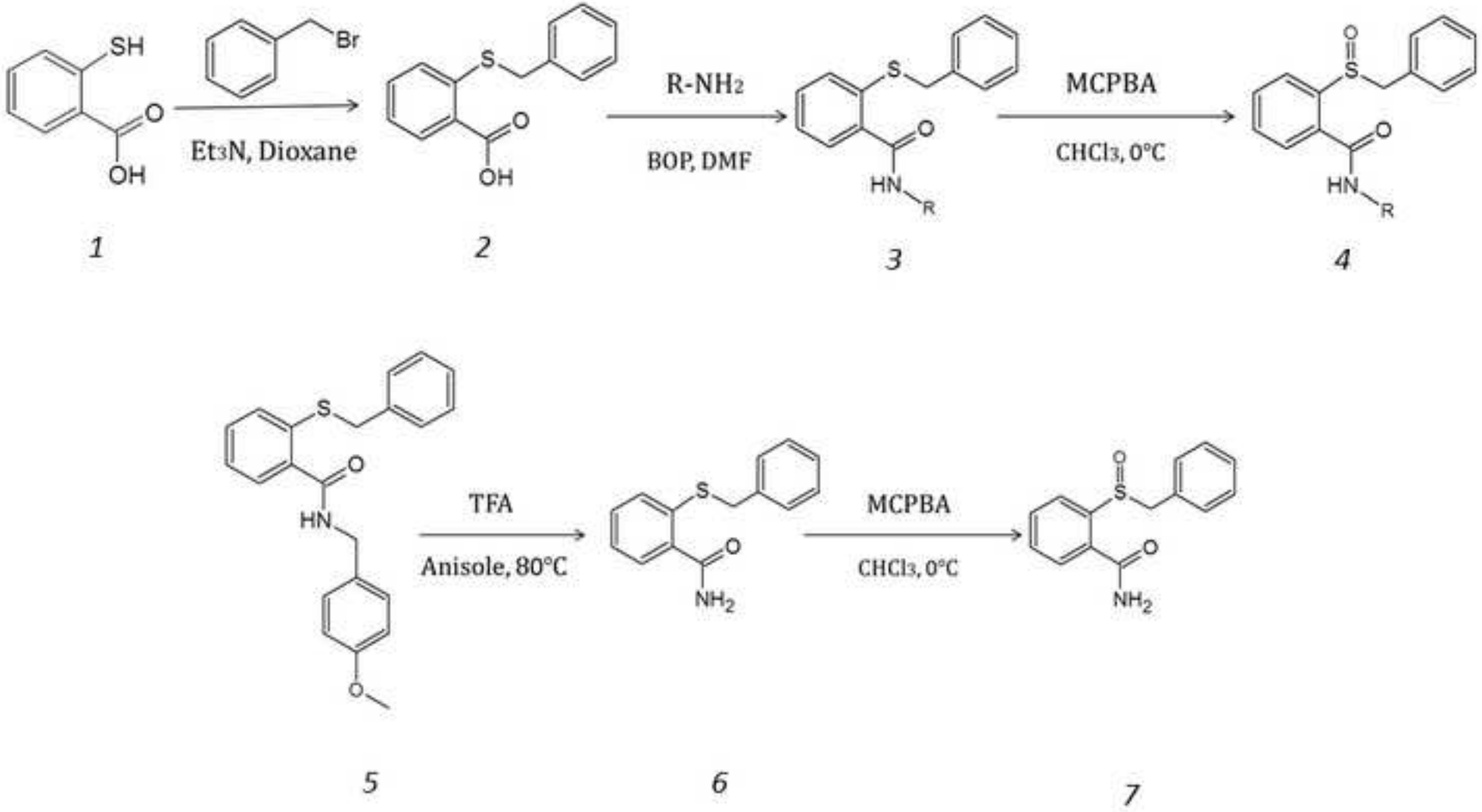

Fig. 2

Figure 3

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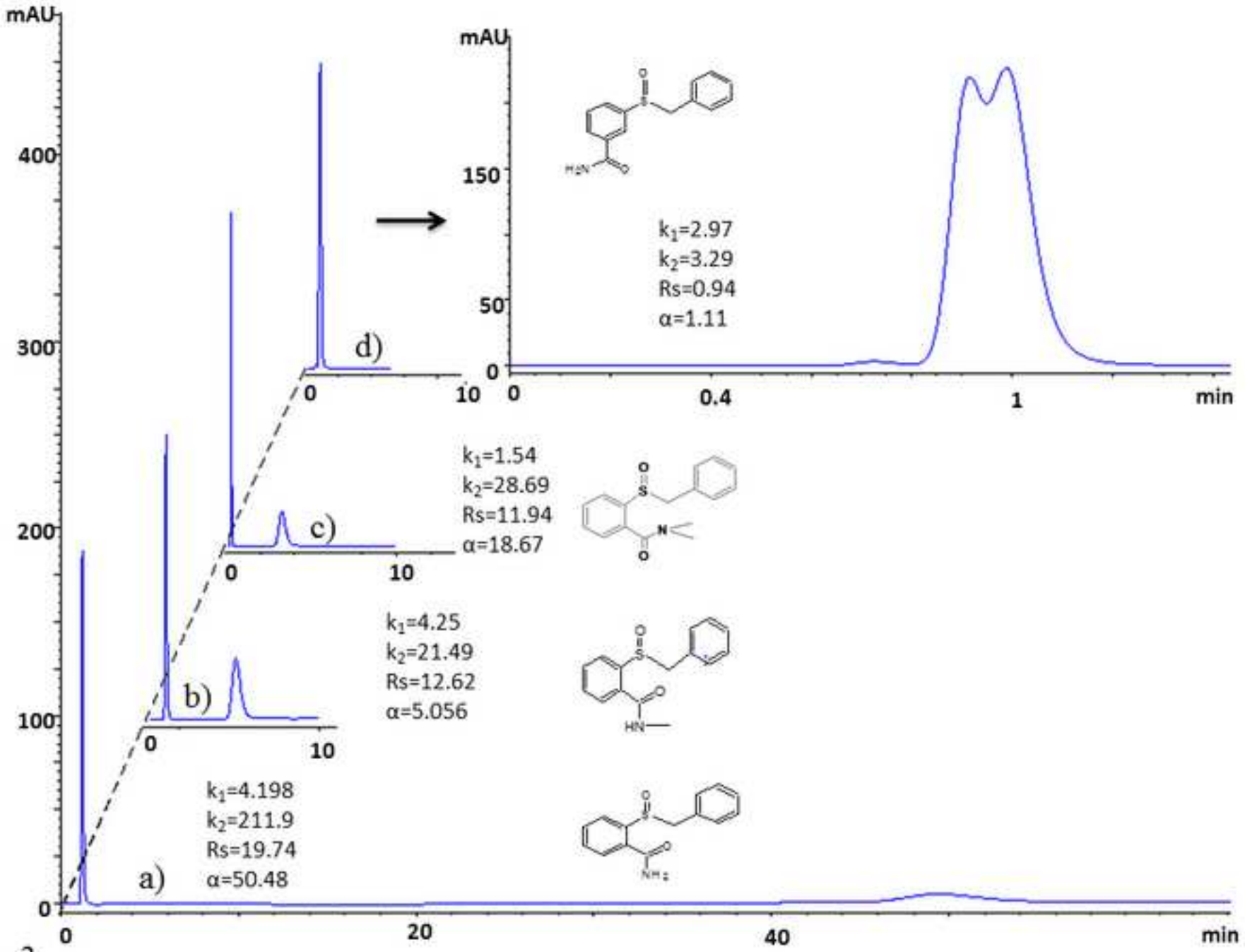

Fig. 3

Figure
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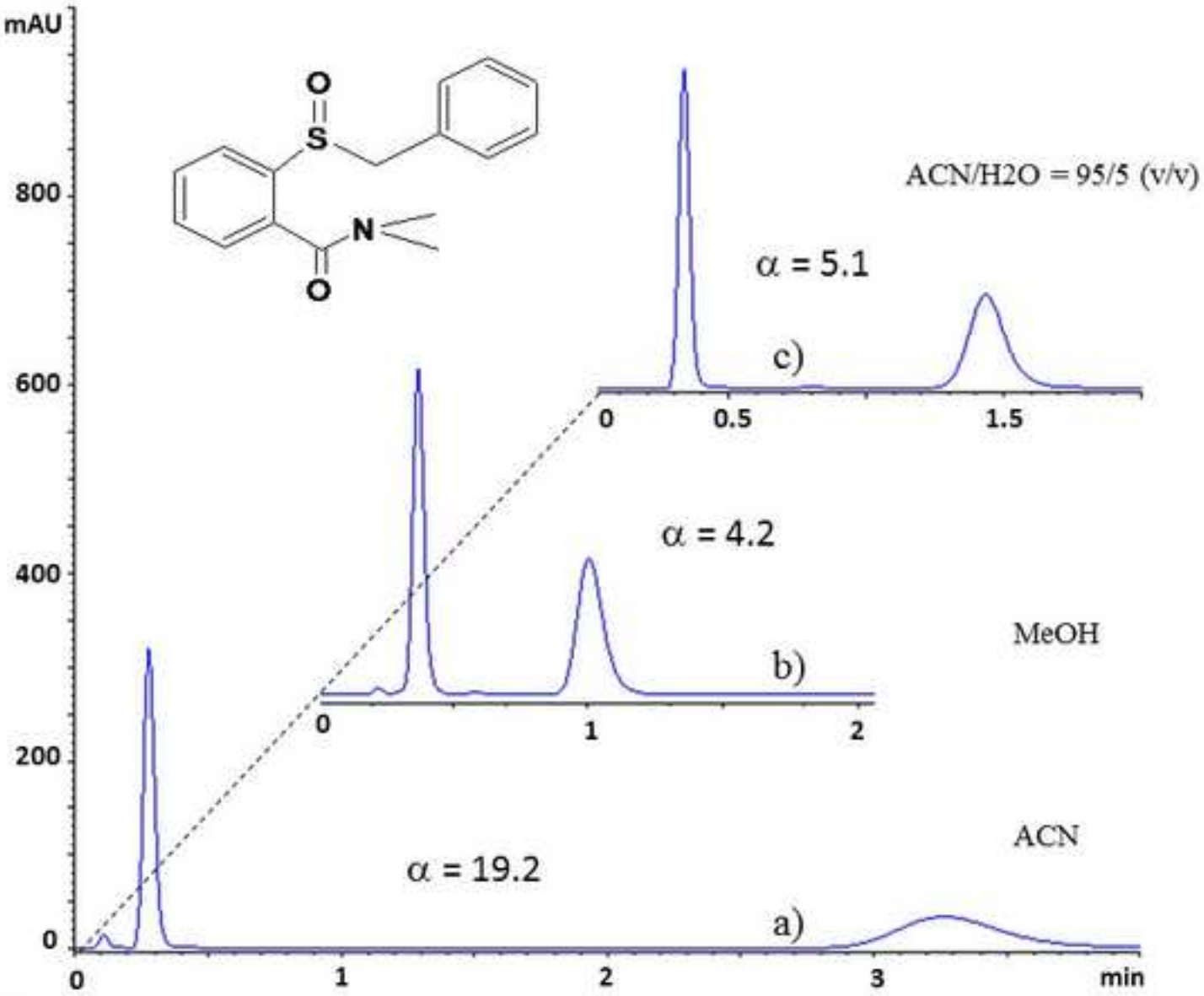

Fig. 4

Figure 5
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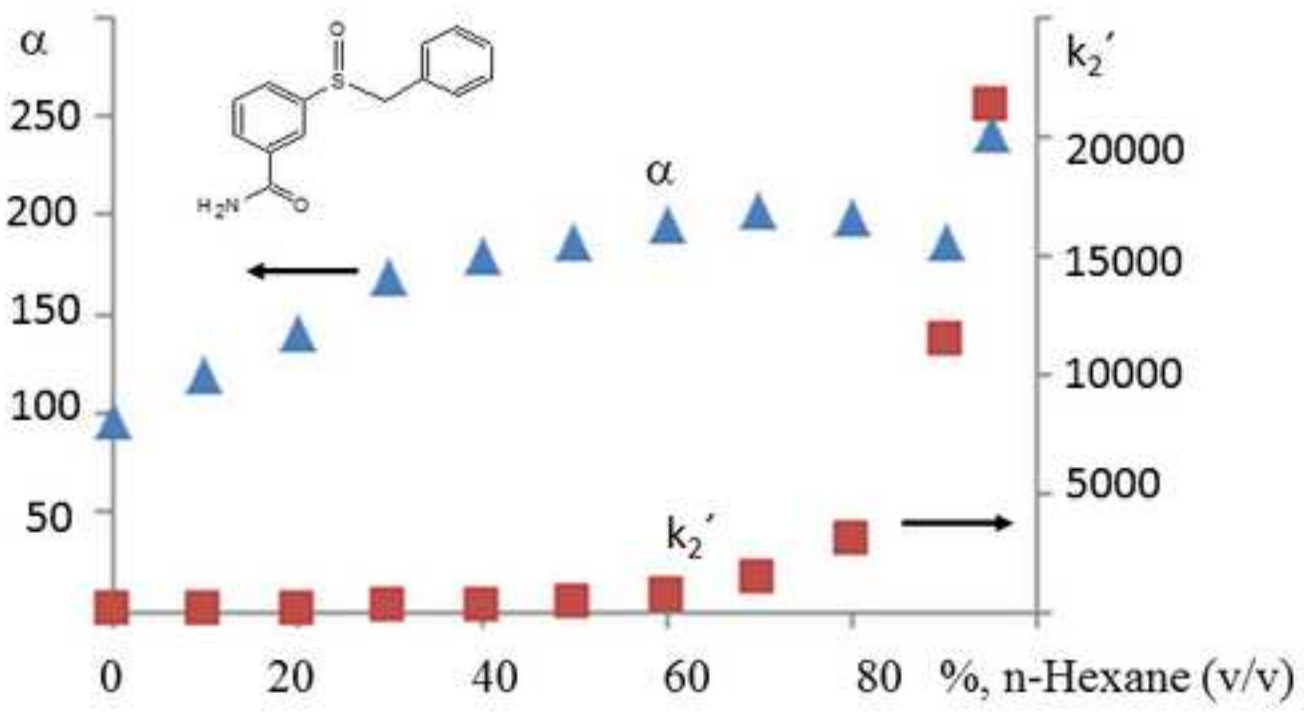

Fig. 5

Figure 6

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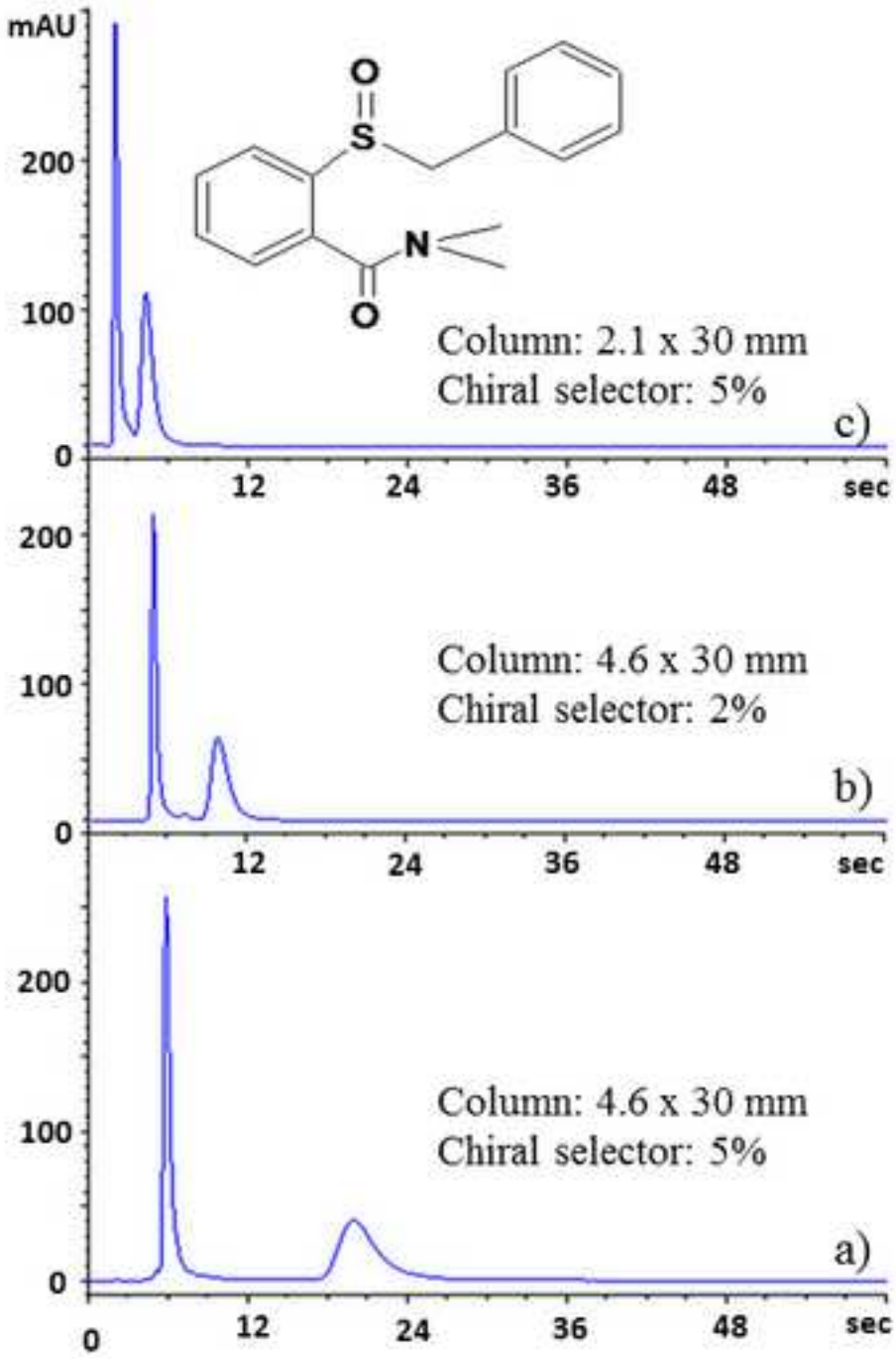

Fig. 6

Figure 7
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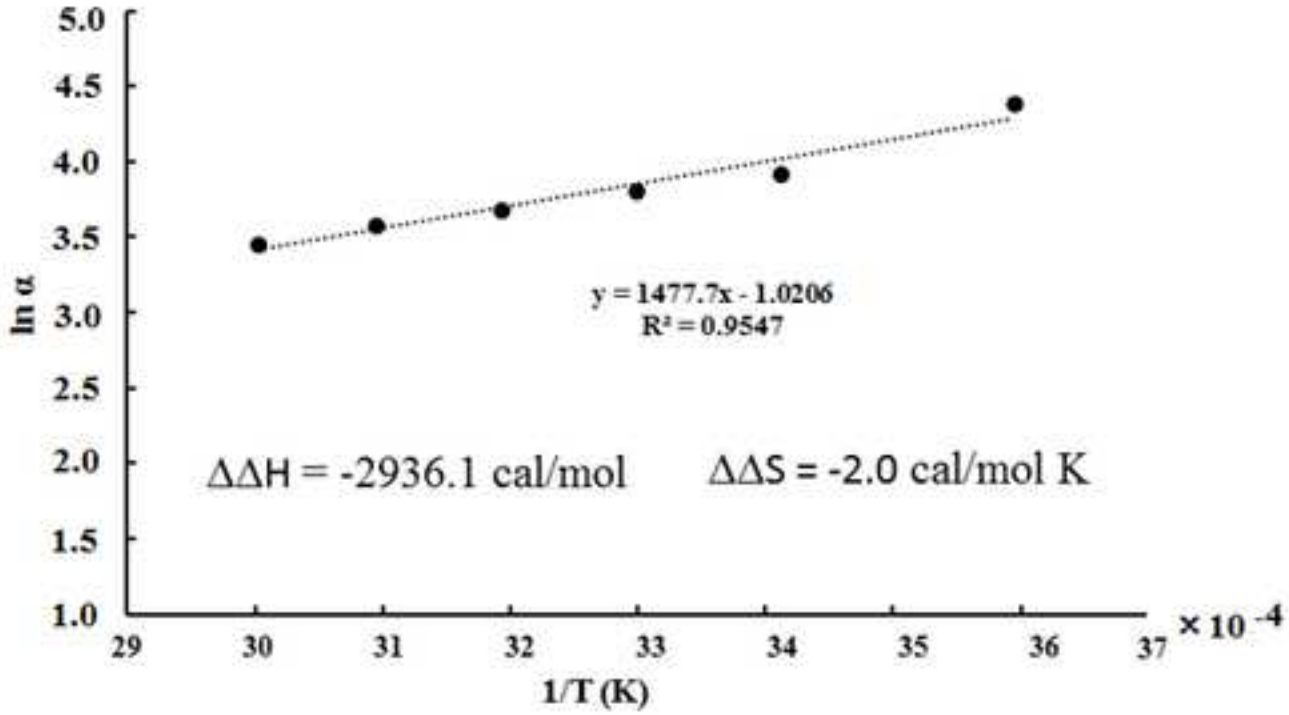

Fig. 7

Figure 8
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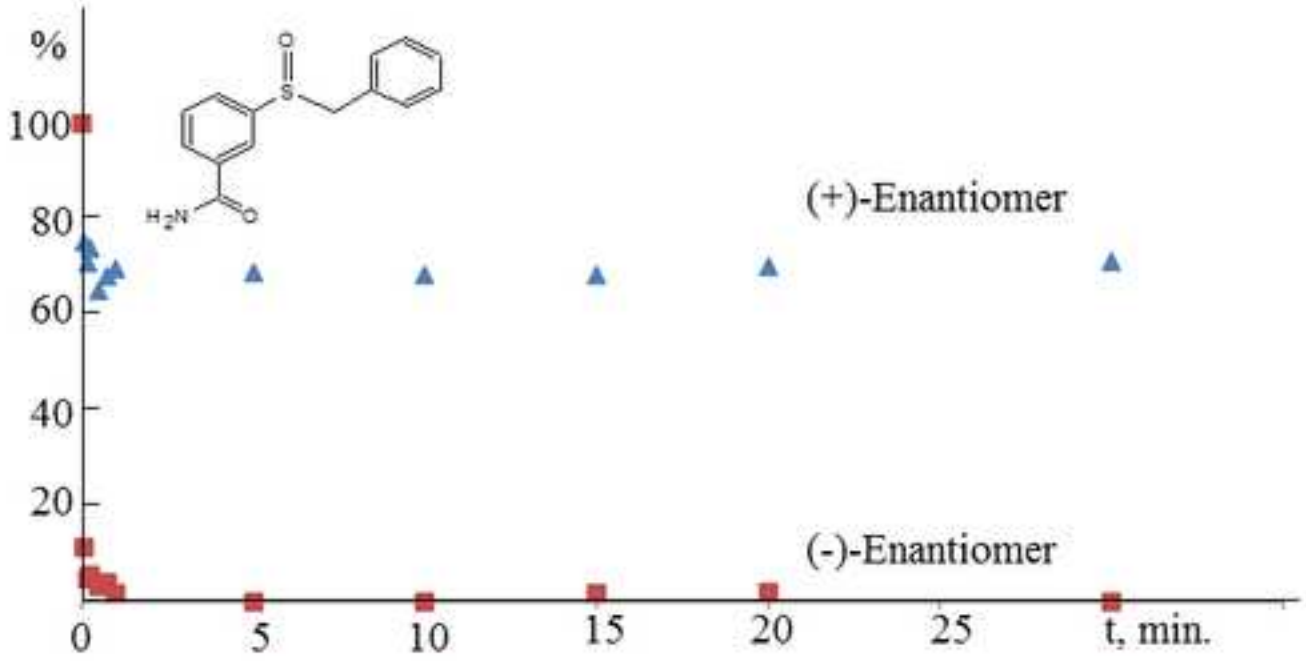

Fig. 8

Figure 9

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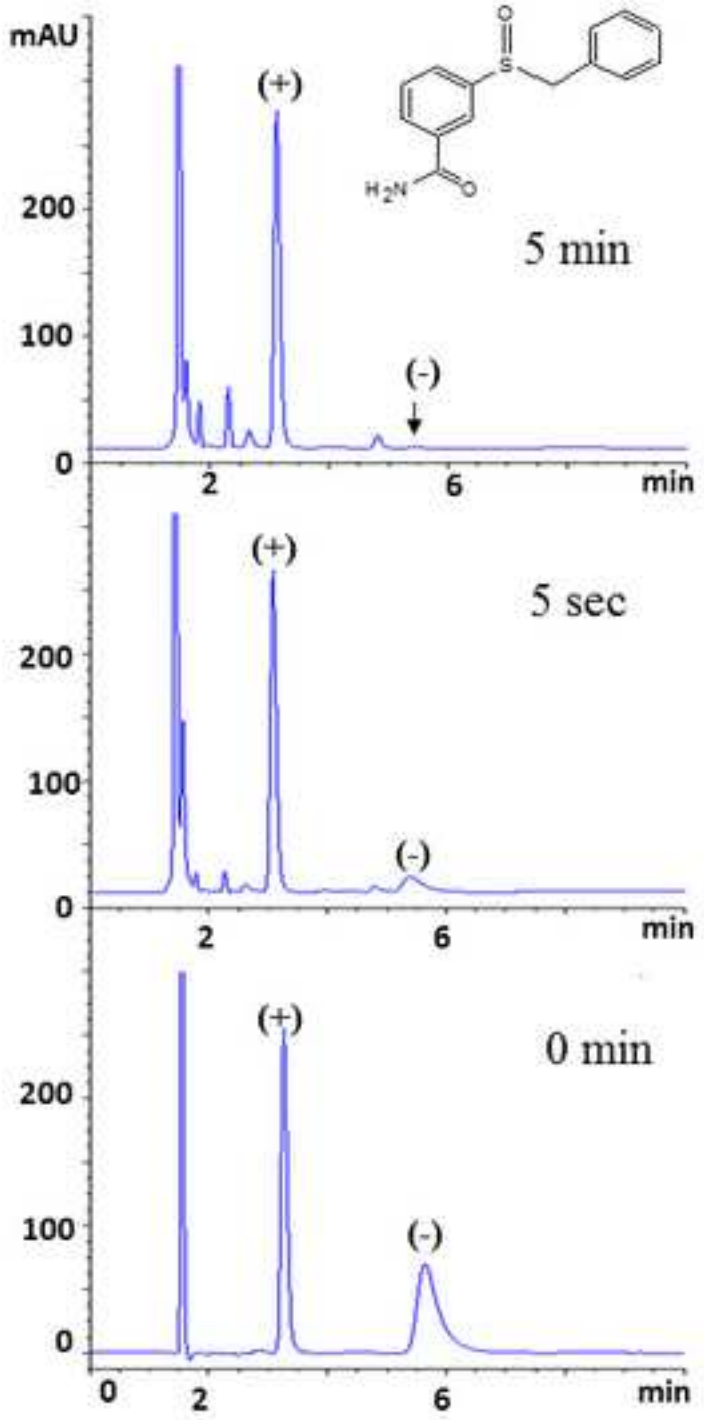

Fig. 9

Table 1

Table 1 Separation results of 5 chiral sulfoxides in 5 mobile phases

Analyte	ACN			MeOH			2-Propanol			2-Prop/ n-Hex=30/70			ACN/H_2O=80/20		
	k_1'	k_2'	α	k_1'	k_2'	α	k_1'	k_2'	α	k_1'	k_2'	α	k_1'	k_2'	α
2-(Benzylsulfinyl)benzamide	4.0	242.1	59.9	0.3	6.2	23.1	0.8	78.1	96.3	6.9	1400	202.6	0.5	13.3	26.0
2-(Benzylsulfinyl) N-methyl benzamide	4.6	27.5	6.0	0.3	1.4	4.1	0.7	10.6	16.0	5.3	129.3	24.3	0.5	3.0	5.6
2-(Benzylsulfinyl) N,N-dimethyl benzamide	2.3	53.5	22.8	0.6	3.1	5.2	1.7	32.5	19.4	8.4	312	37.0	0.5	6.5	13.6
3-(Benzylsulfinyl)benzamide	3.5	3.5	1.0	0.3	0.3	1.0	1.3	1.3	1.0	9	10.9	1.2	0.3	0.3	1.0
3-(Benzylsulfinyl) N-methyl benzamide	3.6	4.7	1.3	0.4	0.4	1.0	1.1	1.1	1.0	6.5	8.0	1.2	0.4	0.5	1.1

Table 2 Experimental data used for calculation of differential enthalpy and differential entropy of adsorption for 2-(benzylsulfinyl)-benzamide on cellulose tris(4-chloro-3-methylphenylcarbamate)-based column (4.6 x 30 mm) from acetonitrile as a mobile phase.

Temperature, K	$1/T \times 10^{-5}$	α	$\ln\alpha$
278.15	359.52	80.35	4.386
293.15	341.12	50.48	3.922
303.15	329.87	44.83	3.803
313.15	319.34	39.63	3.680
323.15	309.45	36.08	3.586
333.15	300.17	31.67	3.455

Table 3

Table 3 Thermodynamic parameters for separation of studied compounds in various mobile phases.

Analyte	ACN			MeOH			2-Propanol			Hex/2-Prop=70/30			Hex/2-Prop = 30/70			ACN/H20=95/5			ACN/H20=80/20		
	ΔΔH, kcal/mol	ΔΔS cal/mol x K	$T_{iso,}$ K	ΔΔH, kcal/mol	ΔΔS, cal/mol x K	$T_{iso,}$ K	ΔΔH, kcal/mol	ΔΔS, cal/mol x K	$T_{iso,}$ K	ΔΔH, kcal/mol	ΔΔS, cal/mol x K	$T_{iso,}$ K	ΔΔH, kcal/mol	ΔΔS, cal/mol x K	$T_{iso,}$ K	ΔΔH, kcal/mol	ΔΔS, cal/mol x K	$T_{iso,}$ K	ΔΔH, kcal/mol	ΔΔS cal/mol x K	$T_{iso,}$ K
2-(Benzylsulfinyl)-benzamide	-2.94	-2.03	1448	-1.37	1.57	-873	-1.71	3.13	-548	-2.36	1.50	-1562	-2.09	2.09	-1002	-2.34	-1.14	2052	-2.71	-2.90	936
2-(Benzylsulfinyl)-N-methylbenzamide	-2.35	-4.60	510	-1.00	-0.60	1660	-1.86	-1.11	1677	-2.05	-1.39	1466	-2.05	-1.58	1297	-2.32	-4.47	519	-2.42	-4.95	489
2-(Benzylsulfinyl)-N,N-dimethylbenzamide	-3.37	-5.33	632	-1.68	-2.42	696	-2.35	-2.32	1009	-2.88	-3.26	881	-2.78	-3.25	854	-3.86	-7.60	508	-4.20	-9.32	451
3-(Benzylsulfinyl)-benzamide	-0.65	-2.00	326	-[a]	-	-	-	-	-	-0.37	-0.88	422	-	-	-	-	-	-	-	-	-
3-(Benzylsulfinyl)-N-methylbenzamide	-1.49	-4.80	310	-	-	-	-	-	-	-0.29	-0.60	477	-	-	-	-4.05	-0.96	420	-0.63	-1.75	359

[a] -: No separation of enantiomers was observed.