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Novel chiral ionic liquids stationary phases for the enantiomer separation of chiral acid by high-performance liquid chromatography

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Abstract

Novel chiral ionic liquid stationary phases based on chiral imidazolium were prepared. The ionic liquid chiral selector was synthesized by ring opening of cyclohexene oxide with imidazole or 5,6-dimethylbenzimidazole, and then chemically modified by different substitute groups. Chiral stationary phases were prepared by bonding to the surface of silica sphere through thioene "click" reaction. Their enantioselective separations of chiral acids were evaluated by high-performance liquid chromatography. The retention of acid sample was related to the counterion concentration and showed a typical ion exchange process. The chiral separation abilities of chiral stationary phases were greatly influenced by the substituent group on the chiral selector as well as the mobile phase, which indicated that, besides ion exchange, other interactions such as steric hindrance, π-π interaction, and hydrogen bonding are important for the enantioselectivity. In this report, the influence of bulk solvent components, the effects of varying concentration, and the type of the counterion as well as the proportion of acid and basic additives were investigated in detail.

KEYWORDS

5,6-dimethylbenzimidazole, anion-exchange, cyclohexene oxide, enantioselectivity, hydrogen bonding, imidazolium, substituent group, π-π interaction

1 | INTRODUCTION

Ionic liquids (ILs) have been known for many years and been applied in many ways, such as catalysis,[1,2] solvents in organic synthesis,[3] or functional materials in separation science,[4,5] and so on, due to their excellent properties such as wide liquids ranges, good thermal stabilities, wide range of viscosities, adjustable miscibility, good solvation characteristic, and reusability.[6-8] Chiral ILs (CILs) are important due to their potential chiral discrimination capabilities. The advent of CILs dates back to 1996 when Herrmann et al synthesized *N*-heteocyclic carbenes of imidazoles.[9] A chiral imidazolium chloride IL was obtained as an intermediate during this reaction. Since then, a large number of CILs have been synthesized by using in many aspects, such as nuclear magnetic resonance (NMR),[10] near-infrared spectroscopy,[11] fluorescence spectroscopy,[12,13] and so on. But the application in chromatography is only more used in gas chromatography, such as Armstrong and coworkers who have done pioneering work in introducing highly thermally stable, uniquely selective, multicationic ILs as gas chromatographic stationary phases.[14-16] The application in high-performance liquid chromatography (HPLC) is much smaller than in gas chromatography. Currently, no more than 10 CIL stationary phases have been reported for HPLC. For example, Li et al prepared four novel chiral stationary phases (CSPs) based on β-cyclodextrin

derivatives functionalized by ILs, having a good performance on aromatic alcohols and ferrocene derivatives.[17] To expand the application of ILs especially for CILs in liquid chromatography, we consider the use of the ion exchange interaction between the liquid cationic groups and anion samples.

Enantiopure drugs are always in high demand due to the different biological and pharmacological activities of drug enantiomers in the pharmaceutical,[18] biological,[19] and other industries. The separation of chiral compounds is particularly important. Especially, the separation of chiral acid is also very vital. In the case of lactic acid,[20] 2-hydroxyglutaric acid,[21] and glyceric acid,[22] changes in enantiomeric proportions play a vital role in disease. Their enantioselective analysis is consequently a major concern in biomarker studies and clinical analysis. Therefore, the development of chiral acid separation method is particularly important.

There are many methods that have been used for the analysis and preparation of acidic samples, such as supercritical fluid chromatography,[23] gas chromatography,[24] liquid chromatography, capillary chromatography,[25] and crystallization.[26] Among them, liquid chromatography is the most widely used. Liquid chromatography is based on the modified silica gel material comprising either immobilized small molecules of chiral selectors (CSs; eg, Cinchona-based ion exchangers),[27] macromolecule CSs (eg, biopolymers or synthetic polymers),[28] or macrocyclic CSs (cyclodextrin antibiotics).[29] The broad family of CSPs has enabled separation of almost any racemic mixture of choice, ranging from neutral lipophilic to highly polar hydrophilic compounds.

In this paper, a novel type of strong anion exchange CSP was synthesized, in which the imidazole IL was immobilized onto the modified silica gel material, as shown in Figure 1. Acidic samples were ionized, with a

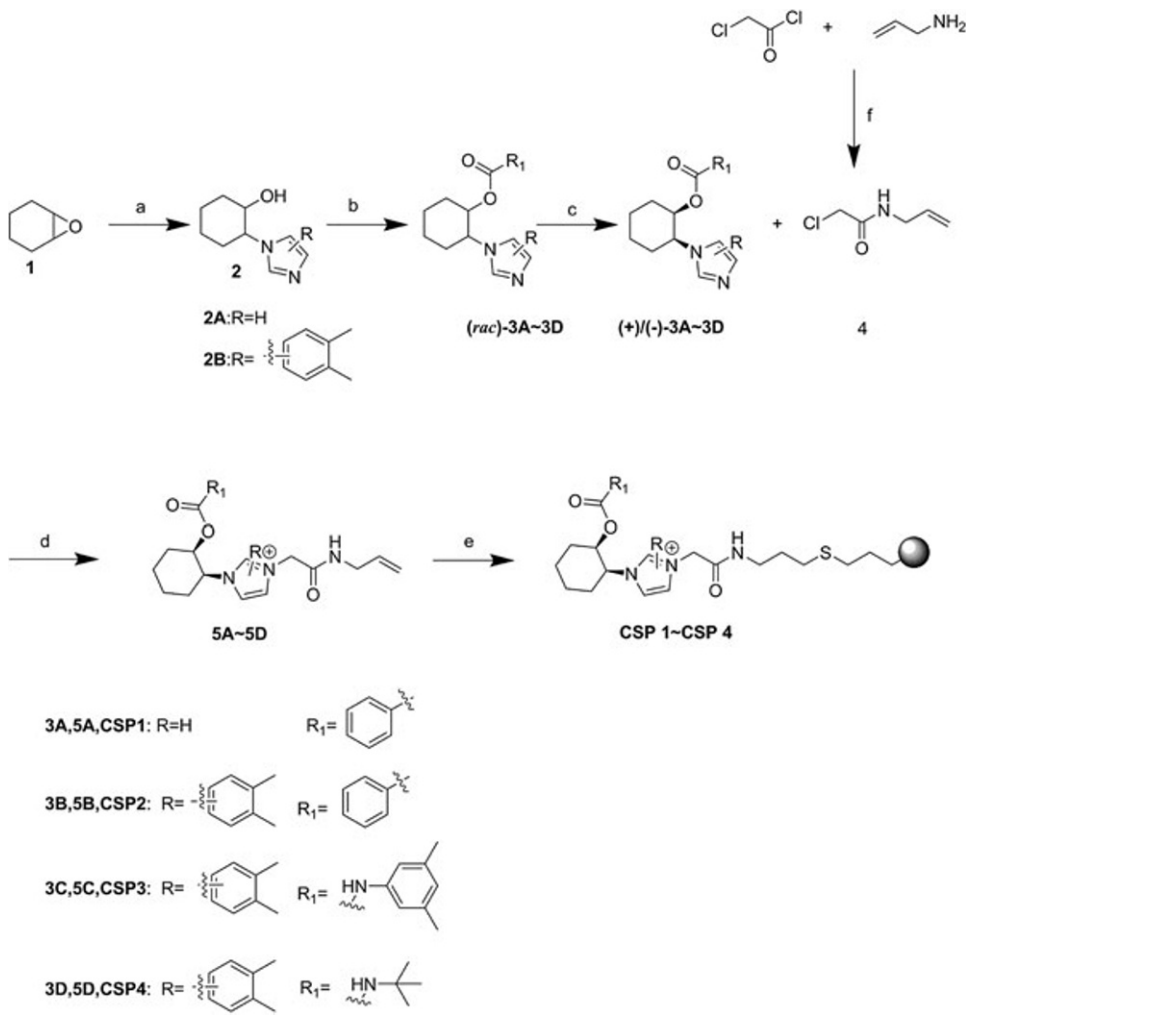

FIGURE 1 The synthesis route of chiral stationary phase (CSP) 1 to CSP4: A, Imidazole or 5,6-dimethylbenzimidazole, 70°C,12 hours; B, Benzoic anhydride, triethylamine, dichloromethane, room temperature, 4 hours; C, preparative enantiomer separation on S-Chiral B, MP:8n-hexane/2-ethanol (vol/vol) (overall yield 80%, >99% ee); D, ACN, 70°C, 24H, N_2, reflux; E, thiol-modified silica gel, azobisisobutyronitrile, methanol, 65°C, N2, reflux; F, EA:H_2O = 1:1, 0°C-rt, 2.5 hours

negative charge, under the mobile phase of acetonitrile (ACN)/50-mmol acetic acid (HAc)/50-mmol triethylamine (TEA) (vol/vol/vol), taking ion interaction with the positive stationary phase. In the separation process of acidic samples on this type of CSP, except the ion exchange, there were π-π interaction and hydrogen bonding interaction.

In addition, in this study, influences of the mobile phase composition concerning acid-to-base ratio as a substitute for proton activity, protic-to-aprotic solvent ratio, and counterion variation on the overall chromatographic performance were investigated to reveal the ion exchange process as the main mechanism for retention and to map the conditions under which this new material can be successfully operated. These aspects will be discussed in detail in the following sections.

2 | MATERIALS AND METHODS

2.1 | Instrumentation

High-performance liquid chromatography-grade spherical silica gel (5-μm particle size; 10-nm pore size; 300-m^2/g surface area) was purchased from Acchrom Technologies (China). ^{1}H-NMR and ^{13}C-NMR identifications were carried out on a Bruker AVANCE 400 (Germany) at a temperature of 25°C. Elemental analysis was measured on an elementar vario EL III (Germany). The CSP of preparation of monomeric compounds was purchased from Acchrom Technologies (China). Other chemicals and equipment are described in the Supporting Information.

2.2 | Chromatographic condition and sample preparation

For evaluation, each CSP 1 to CSP 4 (2.5 g) was slurried in methanol (20 mL) and packed into a 150 × 4.6-mm HPLC column with methanol (100 mL) as propulsion solvent under a pressure of 50 MPa. All the chromatographic separations were performed on Waters HPLC system consisting of a 515 HPLC pump, 2489 UV/Vis detector, 7725i manual injector, and model 1500 column heater (Waters, USA).

All the analytes (AR1-AR10), as shown in Figure 2, used for chiral separation evaluation were dissolved in HPLC-grade ethanol to form about 1-mg/mL concentration. Dead time t_0 was measured with 1,3,5-tri-t-butylbenzene as the void volume marker by using the eluent of methanol. The flow rate was set at 1 mL/min, and column temperature was held constantly at 20°C. Ultraviolet detection wavelength was set at 254 or 220 nm, and the injection volume was 1 μL.

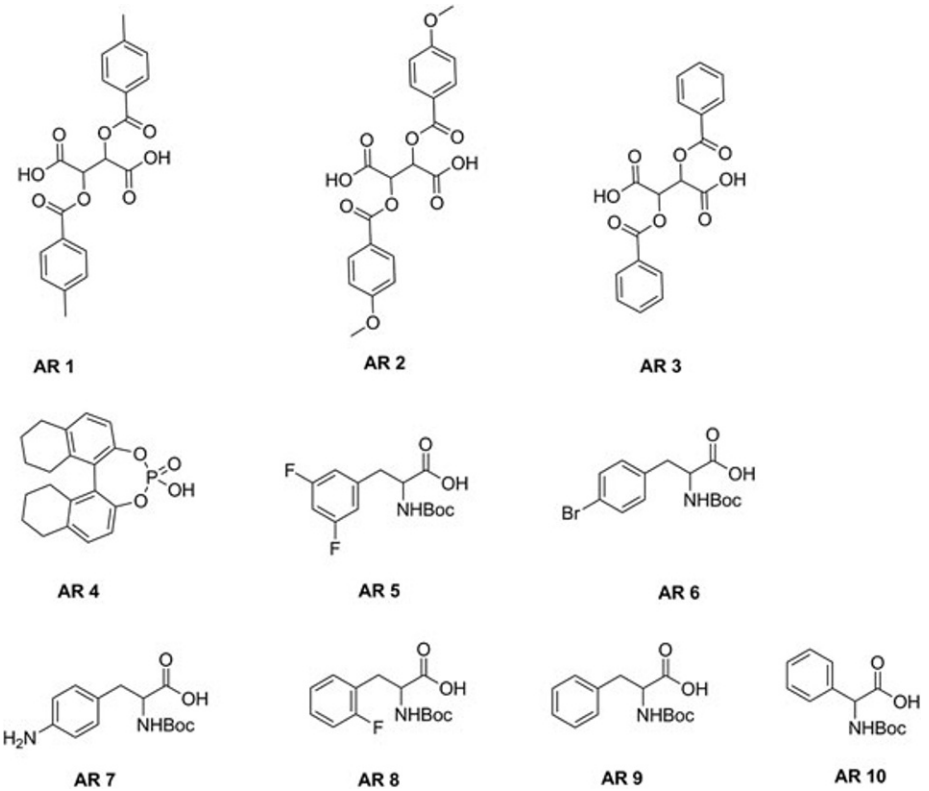

FIGURE 2 The chemical structure of AR 1 to AR 10

Performance of the separation system was monitored in resolution (Rs), selectivity factor (α), and retention time (k_1,k_2), according to the usual formulae:

$$\mathrm{Rs} = \frac{2(t_2 - t_1)}{w_1 + w_2}, \alpha = \frac{k_2}{k_1}, k_1 = \frac{t_1 - t_0}{t_0}, \mathrm{k2} = \frac{t_2 - t_0}{t_0}$$

where t_1 and t_2 are the retention times and w_1 and w_2 are the extrapolated peak widths at the baseline.

2.3 | Preparation of chiral stationary phases

The structures and the synthesis route of CSP 1 to CSP 4 were shown in Figure 1, and the details were shown in the Supporting Information.

3 | RESULTS AND DISCUSSION

3.1 | Preparation of CSP 1 to CSP 4

Strong anion exchangers CSPs 1 to 4 were prepared as outlined in Figure 1, relying on established methodologies. At first, cyclohexene oxide 1 was considered as "spring-loaded" rings for nucleophilic opening reaction with imidazole or 5,6-dimethylbenzimidazole under solvent-free conditions to get the racemic imidazolyl or 5,6-dimethylbenzimidazolyl alcohols 2.[30] Derivation of 2 with different functional group provided the target compounds 3.[31,32] The racemic mixture 3 was resolved chromatographically on a 250 * 20-mm ID column packed with cellulose tris(3,5-dimethylphenylcarbamate) coated silica spheres (S-Chiral B). Typically, on analytical scale, the resolution of racemic 3A to 3D using a normal mobile phase provided excellent selectivity ($\alpha = 2.03$, Rs = 5.68) and the transfer of these conditions to a preparative level allowed high sample loading of 100-mg neat racemate per injection while baseline separation was still maintained. Thus, the collected fractions were virtually enantiopure (data were shown in the Supporting Information). Then, compound 3 was reacted with 4 to afford the target IL 5 and then covalently bonded to thiol-functionalized silica gel through thioene "click" reaction. The loading of CSs corresponding to CSP 1, CSP 2, CSP 3, and CSP 4 were 0.21, 0.16, 0.15, and 0.15 mmol/g according to elemental analysis, respectively (see in the Supporting Information). According to the data of element analysis, it can be seen that the bulkiness of the CSP affects the loading amount.

3.2 | General comparison of CSP 1 to CSP 4

In this paper, four stationary phases were evaluated, mainly to study the effect of steric hindrance, π-π interaction, and hydrogen bond interaction of different derivation groups on chiral separation. The structures of the four stationary phases and the chromatographic results were shown in Figure 1 and Table 1, respectively.

Chiral stationary phase 1 and CSP 2 were prepared by ring opening of cyclohexene oxide with imidazole or 5,6-dimethylbenzimidazole, respectively, and then substituted by benzoate group. The only difference of two CSPs was the part of imidazolium moiety. This design was to investigate the effect of cationic moieties on chromatographic behavior. The enantio separations of the samples on CSP 1 are poor. Only AR 4 can be partially separated with selectivity factor value of 1.05. Compared with CSP 1, CSP 2 had better enantio separation result, on which AR1 to AR3 beside AR 4 were separated under the mobile phase of 6H/4 isopropanol (I)/0.2 trifluoroacetic acid (vol/vol/vol) on CSP 2. As shown in the Figure 3A, AR 1 cannot be resolved on CSP 1. It was completely resolved into enantiomers on CSP 2 ($\alpha = 1.15$, Rs = 1.77). More steric hindrance and π-π interaction provided by the cationic imidazolium moiety are the possible reason for the improvement of enantioselectivity.

The effect of substitute group on oxygen atom on the enantioselectivity was also investigated. Chiral stationary phase 3 has the substitution of (3,5-dimethylphenyl) carbamoyl group on oxygen atom and the same imidazolium moiety as CSP 2. These CSPs have much different enantioselectivity from CSP 2. AR4-AR10 that cannot be separated on CSP 2 were resolved a little on CSP 3 under the mobile phase was 8H/2I/50-mmol HAc/50-mmol TEA, as shown in Figure 4A. The retention time of AR1 to AR3 was very long under this mobile phase. Different steric hindrance and the additional side of hydrogen donor site on carbamoyl group may respond for the change of the enantioselectivity.

Compared with CSP 3, CSP 4 was substituted by tert-butyl carbamoyl group on oxygen. The separation factors and plate numbers on CSP 4 are much lower than those on CSP 3, which indicates that π-π interaction provided by the substitution group is favorable for the chiral discrimination of the analytes, as shown in Figure 3B. In summary, the CSP 3 showed the best ability of separation. In addition, compared with the results obtained under normal phase mode (8H/2I/50-mmol HAc/50-mmol TEA), separation factors and plate numbers of the enantiomers are much higher under polar organic mode (ACN/50-mmol HAc/50-mmol TEA), as shown in Figure 4B. Therefore, the next study was based on the polar organic mode.

3.3 | The influence of counterion concentration

The retention of acidic analyte is primarily controlled by ion exchange, which is a characteristic of the investigated

TABLE 1 Enantioseparation of AR 1 to AR 10 on chiral stationary phase (CSP) 1 to CSP 4

		CSP							
Analyte		**1**		**2**		**3**		**4**	
AR1	k_1	13.24	5.71	14.13	6.62	15.52	3.82	17.65	7.83
	α	1	1	1	1.15	1	1	1.02	1.04
	N_1 (m^{-1})	6,493	15,900	7,013	21,260	6,673	2,993	3,833	3,873
	Rs	—	—	—	1.77	—	—	—	—
	MP	A	B	A	B	A	B	A	B
AR2	k_1	7.62	2.81	8.45	3.03	9.89	1.69	11.92	3.52
	α	1	1	1	1.1	1	1	1.01	1.05
	N_1 (m^{-1})	7,713	20,640	13,647	22,640	11,693	3,060	4,993	3,333
	Rs	—	—	—	1.08	—	—	—	—
	MP	A	B	A	B	A	B	A	B
AR3	k_1	13.62	5.75	15.21	6.66	16.81	3.91	18.21	8.05
	α	1	1	1	1.15	1	1	1.02	1.05
	N_1 (m^{-1})	6,647	15,893	6,673	23,853	6,507	2,727	3,660	3,800
	Rs	—	—	—	1.8	—	—	—	—
	MP	A	B	A	B	A	B	A	B
AR4	k_1	9.83	15.02	7.21	17.46	9.12	12.75	10.02	11.41
	α	1.05	1	1.06	1	1.11	1.14	1.02	1.1
	N_1 (m^{-1})	27,680	8,847	13,247	6,767	26,813	4,687	9,833	10,680
	Rs	0.83	—	1.02	—	1.61	0.86	—	0.92
	MP	A	C	A	C	A	C	A	C
AR5	k_1	2.01	6.28	1.52	4.74	1.79	3.95	3.64	7.8
	α	1	1	1	1	1.14	1.15	1.04.	1.12
	N_1 (m^{-1})	14,027	10,720	18,873	16,307	34,087	5,667	8,233	10,080
	Rs	—	—	—	—	1.57	0.83	—	0.95
	MP	A	C	A	C	A	C	A	C
AR6	k_1	2.76	9.35	2.21	6.17	2.65	5.27	3.73	9.5
	α	1	1	1	1	1.17	1.18	1.03	1.15
	N_1 (m^{-1})	11,613	10,120	21,037	10,640	39,433	6,080	8,587	5,967
	Rs	—	—	—	—	2.23	0.92	—	1.01
	MP	A	C	A	C	A	C	A	C
AR7	k_1	3.52	12.01	2.09	7.57	2.75	5.74	4	10.9
	α	1	1	1	1	1.27	1.16	1.06	1.17
	N_1(m^{-1})	8,427	8,993	19,507	9,713	31,993	4,247	8,507	4,667
	Rs	—	—	—	—	3.27	0.86	—	1.03
	MP	A	C	A	C	A	C	A	C
AR8	k_1	2.54	11.41	2.34	6.74	2.05	5.68	3.85	11.05
	α	1	1	1	1	1.19	1.17	1.01	1.15
	N_1(m^{-1})	13,447	9,813	18,640	10,427	33,920	4,607	8,300	6,213
	Rs	—	—	—	—	2.17	0.95	—	1.05
	MP	A	C	A	C	A	C	A	C
AR9	k_1	2.65	13.1	2.54	8.01	2.47	5.18	4.07	10.82
	α	1	1	1	1	1.21	1.19	1.03	1.14
	N_1 (m^{-1})	14,240	8,320	17,927	10,127	29,200	14,040	8,427	7,027
	Rs	—	—	—	—	2.52	1.01	—	1.04
	MP	A	C	A	C	A	C	A	C
AR10	k_1	2.68	12.52	2.46	7.68	2.41	5.45	4.14	10.62
	α	1	1	1	1	1.15	1.15	1.05	1.14
	N_1 (m^{-1})	14,767	8,747	18,327	10,893	31,720	4,773	7,853	7,047
	Rs	—	—	—	—	1.65	0.85	—	1.04
	MP	A	C	A	C	A	C	A	C

MP: mobile phase; A: acetonitrile/50-mmol HAc/50-mmol triethylamine (TEA); B: 6H/4I/0.2 trifluoroacetic acid (vol/vol/vol); C: 8H/2I/50-mmol HAc/50-mmol TEA.

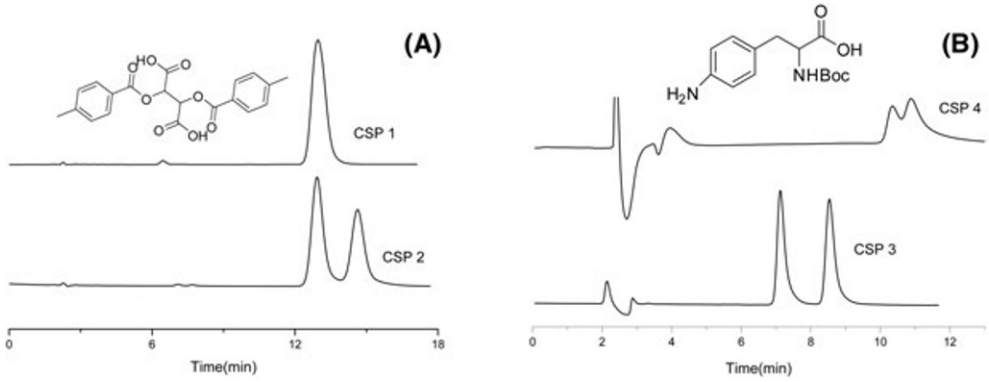

FIGURE 3 High-performance liquid chromatography of AR 1 and AR 7: A, mobile phase: 6 hexane/4 isopropanol/0.2 trifluoroacetic acid, analyte: AR 1; B, mobile phase: acetonitrile/50-mM HAc/50-mM triethylamine, analyte: AR 7. Flow rate: 1.0 mL/min, *T*: 25°C, UV detection at 254 nm

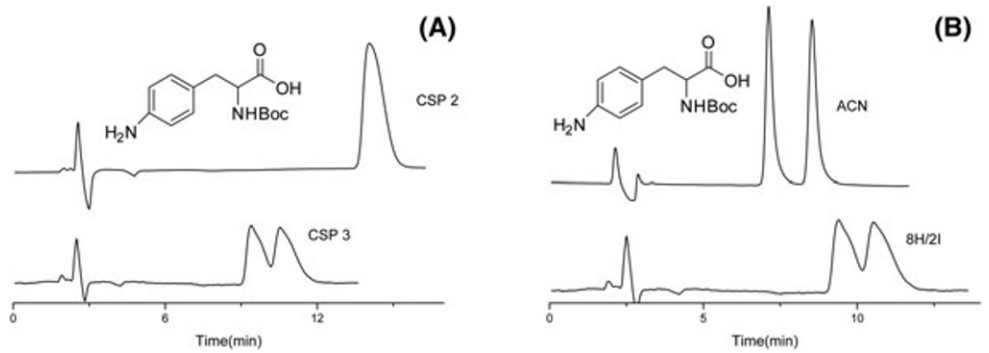

FIGURE 4 High-performance liquid chromatography of AR 7: A, mobile phase: 8H/2I/50-mmol HAc/50-mmol triethylamine (TEA); B, stationary phase: CSP 3, mobile phase: acetonitrile/50-mmol HAc/50-mmol TEA and 8H/2I/50-mmol HAc/50-mmol TEA. Flow rate: 1.0 mL/min, temperature: 25°C, UV detection at 254 nm

CSPs. A near neutral polar organic mobile phase system was applied to investigate the ion-exchange property of the CSPs. Equivalent molar ratio of acid and basic additive were added to the mobile phase to evaluate the stationary phase. Under such conditions, the acidic analytes are protonated while the CSPs are cationic. Thus, the ion exchange between the cationic stationary phase and the anionic analyte is the predominant interaction leading to the retention and separation of the analytes. Chiral stationary phase 3 was taken as an example to explore the existence of ion exchange. Counterion concentrations were varied in the range of 20 to 50 mmol. The results obtained were depicted as plots of the logarithm of the retention factors (log k_1) versus the logarithm of counterion concentration of the first eluted enantiomer (log c) (Figure 5A).

As the concentration of counterions increased, the retention time decreased. The linear relationship between log k and log c can be observed. This phenomenon clearly indicates that the retention of these analytes on the CSP was mainly due to the effect of ion exchange interaction according to a stoichiometric displacement model.[33] The ratio of solute to counterion effective charge determines the slope of the curve. Under the given mobile phase conditions, it is expected that both the analyte and the counterion are protonated and have equivalent isoelectric charge. Chromatographic data demonstrated that the plot showed very similar slopes of log k_1 versus log c plots of 0.95 to 1.05. The first and second eluted enantiomers exhibited almost the same slope (data not shown), indicating that the two isomers had the same type of ion exchange process in the column and respond equally to changes in counterion concentration. Thus, the selectivity does not change significantly with the change of the concentration of the counterion (Figure 5B). The independence of selective on counterion concentration is a unique feature of these novel stationary phases that depend on the ion exchange process and can adjust the retention time without affecting the selectivity.

3.4 | Variation of the acid-to-base ratio

The proton activity of the mobile phase can also affect the ion exchange process by adjusting the degree of ionization of the analyte. To explore the appropriate operating

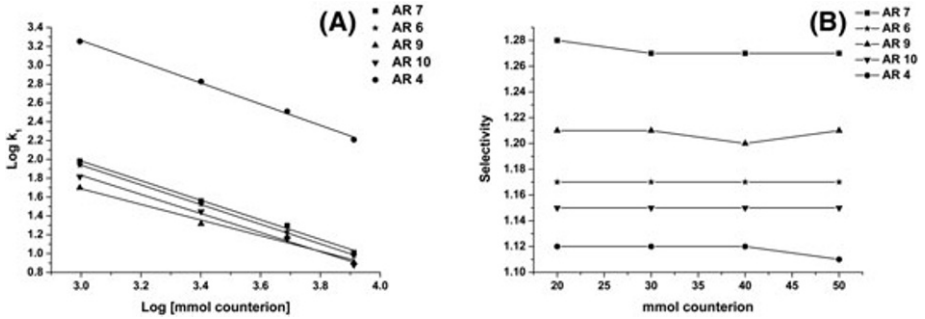

FIGURE 5 Influence of the counterion concentration on (A) retention of the first eluting enantiomer and (B) selectivity. The data of five representative chiral analytes are shown

conditions, the dependence of CSP 3 on the mobile phase with different acid-to-base ratio was studied. For this purpose, six different acid-to-base molar ratios of the mobile phase additive components were selected by using HAc and TEA in an ACN solvent system. Besides equimolar conditions, the acidic conditions are expressed by the ratio of acid to base 1.2/1, 1.4/1, 1.6/1, 1.8/1, 2/1 (60, 70, 80, 90, and 100-mmol HAc and 50-mmol TEA). The retention and the selectivity of representative acidic species for different acid-base ratio mobile phases were shown in Figure 6.

As the alkaline mobile phase affects the life of the stationary phase, it is not used. It can be seen that the retention of analytes had a slight decrease as the proportion of acid additives in the mobile phase increased but constant concentration of the basic counterion. This is because the extra acidic additives inhibited the ionization of the acidic sample, resulting in the ion-exchange interaction between the sample and the stationary phase reducing (Figure 6A). The capacity of the strongly basic ion exchange sites on CSP 3 did not decrease. And there was also a slight reduction in selectivity (Figure 6B). Thus, the equivalent phase of the acid-base ratio of the mobile phase was selected to use for the further study. It can be concluded from Figure 6 that the stationary phase of a strong anion exchange mode such as CSP3 has a broad prospect in resolving acidic compounds.

3.5 | Variation of the type of acidic counterion

The counterion in the mobile phase is a competitor to the analyte and stationary phase in the ion exchange equilibrium, and therefore, it plays an important role in ion exchange reaction. It is for this reason that, as described in the previous section, the retention time of the analyte

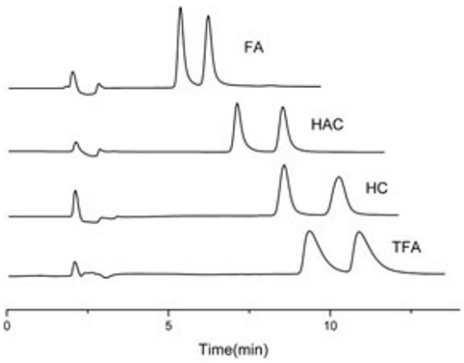

FIGURE 7 Effect of the nature of the counterion being formic acid, acetic acid, trifluoroacetic acid, n-hexanoic acid, and trimethylacetic acid. Data of a representative chiral analyte AR 7 are shown. CSP 3; *T*: 25°C, flow 1.0 mL/min, UV detection at 254 nm, mobile phase: formic acid, HAc, n-hexanoic acid, trifluoroacetic acid (50 mM), and diethylamine (50 mM) in acetonitrile

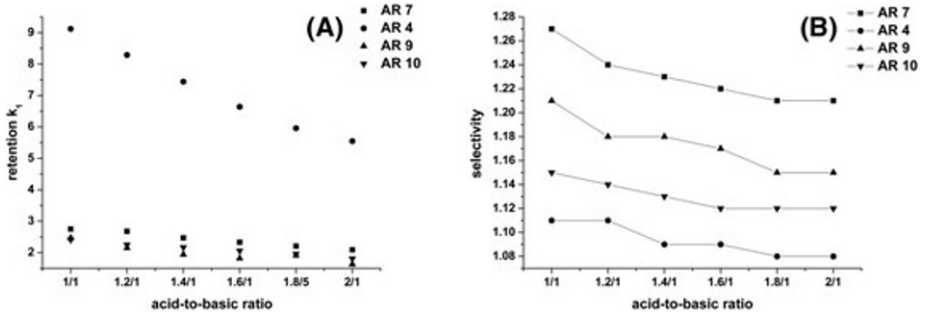

FIGURE 6 Effect of the acid-to-base molar ratio on (A) retention and (B) selectivity. Data of five representative chiral analytes are shown. CSP 3: *T*: 20°C, flow 1.0 mL/min, UV detection at 254 nm, mobile phase: triethylamine (50 mM), and HAc (60, 70, 80, 90, and 100 mM) in acetonitrile

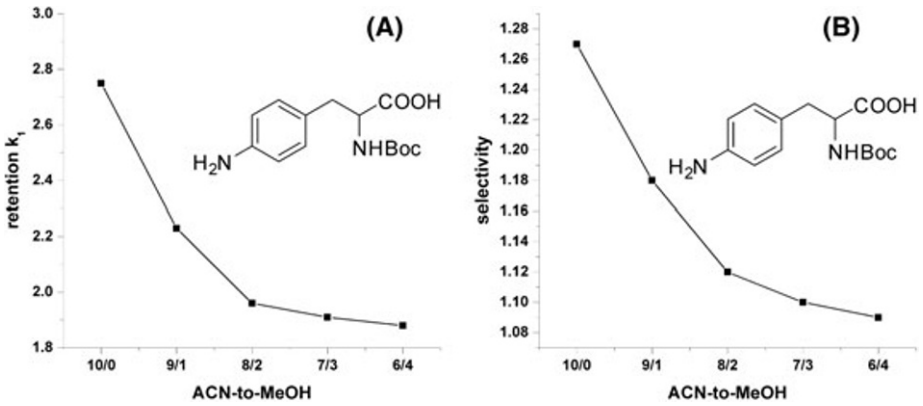

FIGURE 8 The effect of the acetonitrile-to-MeOH ratio on (A) retention and (B) selectivity. Data of AR 7 are shown. CSP 3: *T*: 20°C, flow 1.0 mL/min, UV detection at 254 nm, mobile phase: triethylamine (50 mM) and HAc (50 mM) in acetonitrile/methanol

can be varied by changing the ion concentration. However, not only the concentration, the type of counterion will also affect the chromatographic behavior. In the study of anion exchange stationary phase such as quinine, the type of acid additive also affects the retention of acidic samples.[34] In this experiment, formic acid (pKa = 3.74), HAc (pKa = 4.74), trifluoroacetic acid (pKa = 0.23), and n-hexanoic acid (pKa = 4.86) as counterion were selected to investigate the effect of the type of ions on the retention and selectivity of acidic samples.

It can be deduced from Figure 7 that the type of counterion did change the retention of the analyte, and as the retention time increased, the peaks were wider and the tailings more severe. Furthermore, as a consequence of the ion exchange process, the retention of the analyte can be regulated either with changes of the counterion type or its concentration. Except the retention time, the selectivity and resolution were affected by the variation of the type of counterion, although just a small extent. Selectivity and resolution of the best is acetic acid as a counter ion, the selectivity of 1.27, the resolution of 3.27.

3.6 | Influence of protic and aprotic solvent components

It is well known that methanol and ACN are the preferred organic solvents for nonpolar organic models. Methanol is a proton solvent that affects the hydrogen bond between the analyte and the stationary phase, while ACN is an aprotic solvent which has a π-π shielding effect. Therefore, it is very meaningful to examine the effect of organic solvents on the behavior of such stationary phase chromatography.

For this purpose, the proportions of ACN and MeOH in the mobile phase were varied (10/0, 9/1, 8/2, 7/3, 6/4, and 0/10, ACN/MeOH) under otherwise identical conditions. From Figure 8, we can conclude that the selectivity of the analyte is greatly reduced along with the increase in methanol content, and the selectivity of the analyte exhibits a linear decrease with the increase of the methanol content (Figure 8B). This indicates that methanol significantly affects the hydrogen bond between the analyte and the stationary phase, so methanol should be avoided when selecting the mobile phase. In addition, the retention time decreases as the methanol content increases, because the polarity of the methanol is greater than that of ACN, increasing the strength of the elution, and therefore, the retention is reduced (Figure 8A).

4 | CONCLUSION

In this study, a type of novel CIL stationary phase based on chiral imidazole was designed. The CSPs showed efficient enantioseparation effect on a number of chiral acids. Evaluation of chromatographic data revealed that even fine changes in the CS structure and mobile phase properties can lead to large differences in retention and enantioselectivity of the applied systems. The imidazolium cation site in IL CS played a key role in the process of chiral separation, and its ion exchange characteristic was evaluated. The chromatographic evaluation also proved that other interactions such as steric hindrance, π-π interaction, and hydrogen bonding are essential in the process of chiral separation besides ion exchange interaction. In addition, based on the observations of the preliminary HPLC runs, the best suitable mobile phase for this type of CSPs was polar organic mode, which can provided much better peak resolutions for the enantiomers.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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