ChemPubSoc Europe

DOI: 10.1002/cplu.201300229

Cyclodextrin-Based Ionic Liquids as Enantioselective Stationary Phases in Gas Chromatography

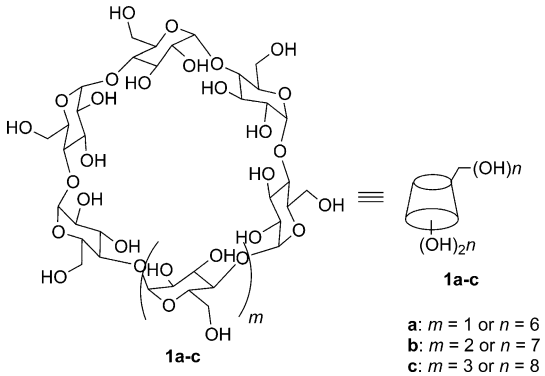
Nuno Costa, Sara Matos, Marco D. R. Gomes da Silva, and M. Manuela A. Pereira*[a]

New permethylated mono-6-deoxy-6-pyridin-1-ium and mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-α- and -β-cyclodextrin trifluoromethanesulfonate ionic liquids were synthesized from the corresponding permethylated mono-6-hydroxycyclodextrins in a one-pot reaction and solvent-free procedure. Regioselective transformation of native α- and β-cyclodextrins with the use of a bulky *tert*-butyldiphenylsilyl protecting group afforded the desired 6-monosubstituted permethylated cyclodextrin derivatives in moderate yields. The new ionic liquids were tested as stationary phases in capillary GC columns towards chiral discrimination in enantio-GC analysis of racemic mixtures. The permethylated 6-deoxy-6-pyridin-1-ium-α-cyclodextrin trifluoromethanesulfonate displayed good enantiomeric separations for some racemic esters and lactones, as well as epoxides. In particular, for both the racemic whiskey lactone and the high boiling point menthyl laurate, not successfully separated in a commercial cyclodextrin phase, the enantiomeric separations were achieved isothermally at 140 °C.

Introduction

Cyclodextrins (CDs) are very popular cyclic oligosaccharides that are used widely in organic syntheses. CDs can bind substrates and catalyze chemical reactions with high selectivity[1] as well as transfer hydrophobic molecules into environmentally friendly medium by supramolecular interaction through reversible formation of host–guest complexes,[2] and have been used as nanoreactors in various organic reactions representing a significant moiety of artificial enzymes.[3]

CDs are naturally occurring water-soluble concave molecules possessing hydrophobic cavities. They are made up of six, seven, or eight glucopyranosidic units linked in an α-1,4 fashion to form α- (**1a**), β- (**1b**), or γ-CDs (**1c**), respectively (Scheme 1). All three common CDs have a similar truncated cone shape,[4] and such a geometry arranges all primary hydroxyl groups (6-OH groups) of the glucopyranosyl units to the narrower end (primary rim) of the cone;[5] consequently, between 6-OH groups of the adjacent pyranose units, there is only a limited amount of space available. Chemical modification of CDs with various functional groups has been investigated extensively.[6] Selective modifications of the CDs are difficult to control because of problems arising from steric and statistical factors imposed by the torus structure and the large number of hydroxyl groups. Usually, if a monofunctionalized CD is synthesized, positional isomers and homologous derivatives with a higher degree of substitution are formed.[7]



Scheme 1. α-, β-, and γ-cyclodextrins **1a**, **1b**, and **1c**, respectively.

CDs have the ability to form inclusion complexes with a variety of chiral compounds and are heavily exploited in chiral recognition and/or resolution of racemic compounds in natural products[8] and the pharmaceutical,[9] agrochemical, and food industries, in which they are employed either as mobile phase additives or chiral stationary phases in high-performance liquid chromatography (HPLC)[10] and gas chromatography (GC).[11]

Also, ionic liquids (ILs) have found many applications in a variety of research areas. Emerging as possible substitutes for volatile organic solvents, ILs have become important as a new reaction medium for chemical and biochemical transformations[12] and also in analytical[11g,13] and separation techniques applications.[14] Their unique properties and chemical stability[15] make ILs intrinsically excellent candidates for industrial solvent applications in contrast to conventional ones and offer great potential to develop clean catalytic technologies. Compared with traditional production methods, the new technologies integrated with ILs ensure many advantages, including short reaction times, mild reaction conditions, simplified opera-

[a] *Dr. N. Costa, Dr. S. Matos, Prof. M. D. R. Gomes da Silva, Prof. M. M. A. Pereira*
REQUIMTE, Chemistry Department
Faculdade de Ciências e Tecnologia
Universidade Nova de Lisboa
2827-516 Caparica (Portugal)
Fax: (+351) 212958300
E-mail: manuela.pereira@fct.unl.pt

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cplu.201300229.

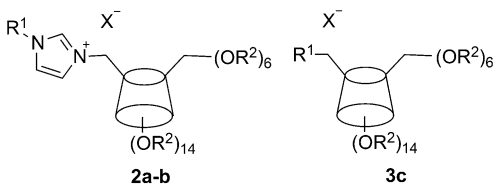
tion procedures, high yields and selectivity, ease of product separation, and recyclability of catalysts and ILs.[16]

As a result of their dual behavior, ILs are receiving increased interest from the chromatography community for multiple tasks. They can separate nonpolar and polar compounds depending on whether they are used to produce apolar or polar phases, respectively.[14b,17] Their unique properties, such as high thermal stability and efficiency on the column, are used to improve gas and liquid chromatographic techniques.[18] The diversity of potential candidates is very wide, because their composition, and consequently the properties displayed, depends exclusively on the cation and anion combinations. These are virtually unlimited. Recently, a comprehensive review was published containing structures and physical properties of a diversity of chiral ILs that have been synthesized during the last six years.[19] Applications in the fields of asymmetric organic synthesis, spectroscopy, and chromatography are also reported.

ILs with trifluoromethanesulfonate anions are of interest for practical applications in various fields. In general, trifluoromethanesulfonate ILs are hydrolytically stable and have fairly low viscosity, and are typically prepared by means of the metathesis reaction of the corresponding chlorides, bromides, or methyl sulfates with metal trifluoromethanesulfonates.[20]

In the last decade, chiral ILs synthesized from carbohydrates have found synthetic and analytical applications.[21] ILs derived from isomannide and isosorbide were used as chiral catalysts in phase-transfer reactions,[22] and a 6-deoxy-6-imidazolium salt derivative from β-CD was used in the asymmetric reduction of acetophenones providing alcohols in high enantioselectivity.[23] A broad range of fundamental free-radical reactions employing the β-CD IL mono-6-deoxy-6-(1-methyl-1*H*-imidazol-3-ium)-β-cyclodextrin tosylate (**2a**) was investigated (Scheme 2).[24] The low solubility of carbohydrate ILs in organic solvents was explored in the IL-supported synthesis of oligosaccharides as an alternative process to the classical solid-phase synthesis.[25]

Cationic CDs containing imidazolium-, pyridinium-, or ammonium-substituted β-CD derivatives were used as chiral selectors or chiral additives for capillary electrophoresis and have demonstrated efficient enantioseparations for some aromatic carboxylic acids.[26] Applications in chiral stationary phases for HPLC and supercritical fluid chromatography (SFC) of different derivatives of cationic CDs were reported.[27] There are not many cases described so far in which chiral ILs are synthesized and used for chromatographic purposes.[28] Here again, the



Scheme 2. ILs derived from β-CD. Ts = toluenesulfonyl, Tf = trifluoromethanesulfonyl.

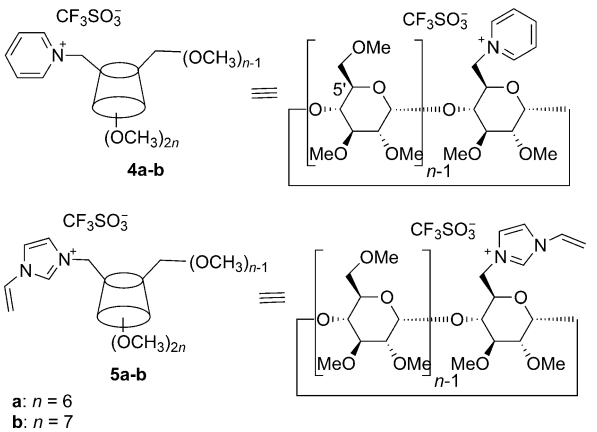
cation or the anion or even both can be responsible for the chiral characteristic of the molecule. Recently, Armstrong and co-workers[29] used charged CDs as a GC chiral selector. Permethylated mono-6-deoxy-6-(1-butyl-1*H*-imidazol-3-ium)-β-cyclodextrin (**2b**) and permethylated mono-6-deoxy-6-(tripropylphosphonium)-β-cyclodextrin (**3**) paired with iodide, NTf_2, and trifluoromethanesulfonate anions were synthesized and evaluated for optimization of the chiral stationary phase composition. High melting points of the CD salt derivatives prevent the use of these derivatives in the pure form as stationary phases. Application of monosubstituted positively charged CDs as chiral stationary phases in the separation of enantiopure amino acids and anionic analytes demonstrated their potential as chiral selectors in HPLC and SFC.[26b,27]

Results and Discussion

Herein, we are interested in preparing stable room-temperature ILs derived from CDs with different cavity sizes able to be used as chiral selectors in GC. The α- (**1a**) and β-CDs (**1b**) are known as good chiral selectors and the opportunity to introduce an ionic moiety at one C-6 center affording new thermally stable ionic salts of CD derivatives was considered. CD salts melting around 100 °C or below, which behave like room-temperature ILs, could be used as chiral stationary phases in GC.

Ammonium, pyridinium, and imidazolium ILs are the most popular because of their low vapor pressures and low melting points. Herein, new trifluoromethanesulfonic salts of permethylated mono-6-deoxy-6-(pyridin-1-ium)-α-cyclodextrin (**4a**), mono-6-deoxy-6-(pyridin-1-ium)-β-cyclodextrin (**4b**), mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-α-cyclodextrin (**5a**), and mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-β-cyclodextrin (**5b**; Scheme 3) were synthesized by a protection/deprotection strategy.[7,11j,30] This strategy deals with the use of chemo- and/or regioselective reactions from native CDs including four main steps: selective protection of one C-6 hydroxyl group, transformation of the remaining ones, deprotection, and finally, suitable functionalization afforded by nucleophilic displacement.

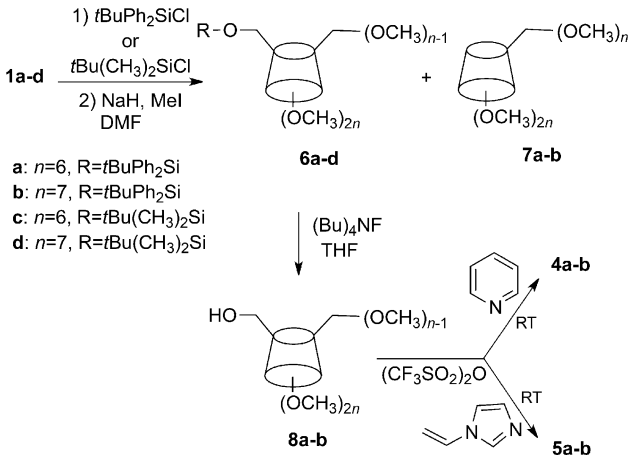
As concerns the permethylated mono-6-*O*-modified CDs, the tosyl group is the most popular protecting group of 6-OH.[3a,31]



Scheme 3. New α- (**4a**, **5a**) and β-CD (**4b**, **5b**) ILs.

Tosylate groups located on the C-6 position in mono-6-*O*-tosyl CD derivatives have been used repeatedly as leaving groups for nucleophilic substitutions, but displacement of the tosylate group requires good nucleophiles, high temperatures, and long reaction times, which yield several byproducts and relatively low yields of the desired monosubstituted compounds.[31b,32] However, the trifluoromethanesulfonate group has been demonstrated to be a better leaving group than tosylate, and nucleophilic substitutions are accomplished at room temperature in shorter reaction times and with better yields.

Regioselective introduction of a trifluoromethanesulfonate group in the primary C-6-OH exclusively in one CD glucopyranoside unit was accomplished by reaction of one primary OH group of native CD with a bulky silyl chloride derivative in the presence of a base, followed by permethylation of the remaining free hydroxyl groups. Further, the permethylated mono-6-*O*-modified CDs required the selective removal of the silyl substituent by reaction with fluoride ion and subsequent introduction of a new leaving group susceptible to displacement by a nucleophile (Scheme 4). Permethylated mono-6-*O*-*tert*-butyldimethylsilyl CDs (**6c**, **6d**) are the most popular mono-6-*O*-modified CD derivatives.[7,33] Even using this bulky *tert*-butyldimethylsilyl substituent, the reactivity of one 6-OH primary group was not selective and the presence of polysubstituted silylated compounds resulted in low yields and tedious purification steps of the desired mono-6-*O*-*tert*-butyldimethylsilyl CD derivatives. Best results were found with the synthesis of *tert*-butyldiphenylsilyl ether, and *tert*-butyldiphenylsilyl chloride was a superior silylating reagent yielding the mono-6-*O*-*tert*-butyldiphenylsilyl derivative of β-CD with reasonable regiospecificity in the one-pot synthesis of permethylated mono-6-hydroxy-β-cyclodextrin (**8b**) as described by Lupescu et al.[30]

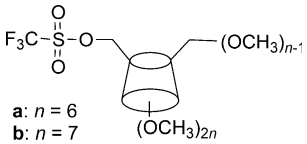


Scheme 4. Synthesis of new ILs **4a**,**b** and **5a**,**b**.

Herein, a modified previous procedure was followed to yield permethylated mono-6-*O*-*tert*-butyldiphenylsilyl-α-cyclodextrin (**6a**). Regioselectivity of primary OH monosilylation is very sensitive to the reaction conditions and the best yield of **6a** was obtained if the CD was reacted with *tert*-butyldiphenylsilyl chloride in DMF and in the presence of imidazole for 1 hour at 60 °C. Although some unreacted α-CD (**1a**) was still present in the reaction mixture, longer reaction times or higher temperatures resulted in the formation of several permethylated polysilylated CD derivatives in complex mixtures. Further, methylation in situ with methyl iodide, after treatment with sodium hydride, yielded the corresponding permethylated mono-6-*O*-*tert*-butyldiphenylsilyl-α-cyclodextrin (**6a**) in 34.4% overall yield, from α-CD. The same procedure was used to obtain the permethylated mono-6-*O*-*tert*-butyldiphenylsilyl-β-cyclodextrin (**6b**). In both transformations some permethylated α- and β-CDs, **7a** and **7b**, respectively, were isolated.

Treatment of **6** with *N*-tetrabutylammonium fluoride in THF at reflux afforded the corresponding permethylated mono-6-hydroxy-CDs **8** after chromatographic purification. To overcome the difficulties of a purification step owing to the presence of tetrabutylammonium salt, the use of NH_4F as fluoride ion source[30] was tested. A longer reaction time and uncompleted transformation were observed if a solution of permethylated mono-6-*O*-*tert*-butyldiphenylsilyl-α-cyclodextrin **6a** in dry methanol was heated at reflux in the presence of an excess of ammonium fluoride for 9 days to yield 67% of the corresponding deprotected α-CD (**8a**).

To accomplish nucleophilic substitution at the C-6 center, the 6-OH group of **8** should be replaced by a good leaving group. Our attention was focused on the trifluoromethanesulfonic ester **9** (Scheme 5) because of its behavior as a good leaving group in nucleophilic displacement at room temperature, and also the possibility of synthesizing it under moderate conditions. The use of trifluoromethanesulfonic esters was supported by their success as an excellent leaving group in nucleophilic substitutions at room temperature.[20] High temperatures should be avoided owing to the thermal lability of CD derivatives.



Scheme 5. Trifluoromethanesulfonic esters **9a** and **9b**.

To obtain the corresponding mono-C-6 trifluoromethanesulfonate derivative **9a**, compound **8a** was reacted with trifluoromethanesulfonic anhydride in dry dichloromethane and in the presence of pyridine at room temperature, as described by Lupescu et al.[30] for the β-CD derivative **8b**. Surprisingly, a very polar compound was formed. After workup and chromatographic purification, the product **4a** (34%) was characterized (Table 1).

One of the most characteristic features of the ^1H NMR spectrum of **4a** demonstrated the presence of the positive aromatic pyridinium ring with the nitrogen atom bonded to the C-6 of one glucopyranose unit of the permethylated mono-6-deoxy-substituted CD (**4a**), in which aromatic protons shifted

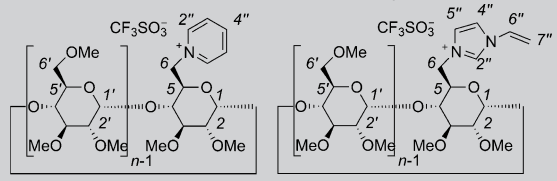
Table 1. Physical data of CD ILs **4** and **5** and compound **8a**.

Compound	Yield [%]	M.p. [°C]	$[\alpha]_D^{21}$ in $CHCl_3$
4a	34[a], 71[b]	84–85	+126.8 ($c=3.0$)[c]
4b	38[b]	110–115	+91.6 ($c=1.4$)[c]
5a	41.5[b]	90–95	+101.9 ($c=3.0$)[c]
5b	29.5[b]	95–99	+117.1 ($c=0.9$)[c]

[a] In dichloromethane. [b] Solvent-free procedure. [c] c is concentration in grams per 100 mL.

downfield and resonated at 9.05 (H-2″), 8.05 (H-3″ and H-5″), and 8.54 (H-4″) (Table 2). The resonance signals of the corresponding two H-6 atoms bonded to the prochiral C-6 atom, 5.30 and 5.19 ppm, of the same glucopyranose unit shifted downfield compared with the precursor compound **8a**, for

Table 2. Typical proton and carbon NMR chemical shifts of CD ILs (**4a,b** and **5a,b**) and **8a,b**. All chemical shift values are given in ppm.



4a-b **5a-b**

a: n = 6
b: n = 7

	4a	**4b**	**5a**	**5b**	**8a**	**8b**
H-6a	5.30	5.35	4.87	4.84	3.98–3.32	3.92–3.72
H-6b	5.19	5.12	4.67	4.61	3.98–3.32	3.92–3.72
H-2″	9.05	9.11	9.27	9.44	–	–
H-3″	8.05	8.06	–	–	–	–
H-4″	8.54	8.54	7.57	7.55	–	–
H-5″	8.05	8.06	7.74	7.80	–	–
H-6″	9.05	9.11	7.34	7.34	–	–
H-7″(*trans*)	–	–	5.77	5.76	–	–
H-7″(*cis*)	–	–	5.46	5.45	–	–
C-6	61.09	61.19	50.51	50.35	62.51	61.82
C-2″	146.72	146.84	137.19	137.53	–	–
C-3″	8.05	8.06	–	–	–	–
C-4″	145.77	145.75	118.18	118.18	–	–
C-5″	127.95	127.71	124.76	124.86	–	–
C-6″	146.72	146.84	128.82	128.86	–	–
C-7″	–	–	110.36	110.13	–	–

which the corresponding protons resonated between 3.98 and 3.32 ppm. Owing to the inductive effect along the sigma bond, the resonance of C-6 was also affected by the positively charged pyridinium ring and its signal shifted upfield by 1.42 ppm. The ^{19}F NMR spectrum confirmed the presence of the trifluoromethanesulfonate anion exhibiting a singlet at −78.3 ppm. To our knowledge, compound **4a** is the first pyridinium room-temperature IL derivative from α-CD, melting at 84–85 °C.

These findings encouraged us to investigate the transformation of permethylated mono-6-hydroxy-α-cyclodextrin (**8a**) and mono-6-hydroxy-β-cyclodextrin (**8b**) with trifluoromethanesulfonic anhydride in the presence of pyridine and other nucleophiles, such as 1-vinylimidazole, in solvent-free procedures.

Typically, trifluoromethanesulfonic ILs are prepared by means of the metathesis reaction of the corresponding chlorides or bromides with metal trifluoromethanesulfonates. Direct alkylation of substituted pyridines with methyl trifluoromethanesulfonate was recently used to prepare halogen-free trifluoromethanosulfonate ILs.[20]

Herein, synthesis of permethylated mono-6-deoxy-6-pyridin-1-ium-α-cyclodextrin trifluoromethanesulfonate (**4a**) was accomplished by the solvent-free reaction of compound **8a** with trifluoromethanesulfonic anhydride in pyridine at room temperature for 2 days to yield 71% of the desired CD IL obtained after chromatographic purification. Following the same procedure the permethylated mono-6-deoxy-6-(pyridin-1-ium)-β-cyclodextrin trifluoromethanesulfonate (**4b**) was obtained from **8b** in 41.5% yield.

The formation of **4** and **5** from **8** can be explained by reaction of **8** with trifluoromethanesulfonic anhydride in the presence of pyridine to form the trifluoromethanesulfonic ester **9**, followed by nucleophilic attack of the pyridine nitrogen at C-6 bonded to the trifluoromethanesulfonate group with consequent displacement of the trifluoromethanesulfonate anion and formation of the corresponding compounds, **4** or **5**, in a one-pot reaction. During the transformation, pyridine or 1-vinylimidazole acted as solvent, base, and nucleophile. This proposal is supported by the presence of trace amounts of the less polar compound **9a**, detected by thin-layer chromatography during the formation of **4a** from **8a** and of compound **9b**, isolated in 38% yield, during the formation of **5b** from **8b** for 38 hours at room temperature. After 3 days at room temperature, and under the same conditions, the yield of **9b** decreased to 18%.

Generally, permethylated mono-6-deoxy-6-(alkyl-1*H*-imidazol-3-ium) salts of CDs were prepared from mono-6-*O*-tosylate CD displacement by the corresponding imidazole nucleophile. Further metathesis of the anion generated the corresponding desired salts. Exploring the basicity and nucleophilic features of 1-vinylimidazole, compounds **8a** and **8b** were treated with trifluoromethanesulfonic anhydride in dry 1-vinylimidazole for 2 days at room temperature to yield the corresponding ILs, the permethylated mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-α-cyclodextrin trifluoromethanesulfonate (**5a**; 41%) and the permethylated mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-β-cyclodextrin trifluoromethanesulfonate (**5b**; 29.5%), respectively.

As anticipated the 6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium) CD trifluoromethanesulfonate salts (**5a** and **5b**) displayed the same ^1H and ^{13}C NMR features as the pyridinium derivatives, **4a** and **4b**, respectively. The protons of the positive imidazolium ring shifted downfield. The more acidic H-2″ resonated at 9.27 and 9.44 ppm. Moreover, vinylic protons resonated at 7.34 (H-6″), 5.77 (H-7″ *trans*), and 5.46 ppm (H-7″ *cis*) with $J_{trans}=15.5$ and $J_{cis}=8.6$ Hz and $J=2.9$ Hz for the geminal coupling constant in compound **5a**, which demonstrated the presence of the vinyl carbon double bound. Moreover, the two protons bonded to prochiral C-6 shifted downfield by 1 ppm, less than in the pyridinium derivative, and the C-6 signal shifted from

62.51 and 61.82 ppm in permethylated 6-mono-hydroxyl α-(**8a**) and β-CDs (**8b**) to 50.51 and 50.35 ppm in 6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium) CD trifluoromethanesulfonate salts **5a** and **5b**, respectively.

As we expected, all CD salt derivatives prepared melted below 100 °C except the β-CD pyridinium trifluoromethanesulfonate **4b** (m.p. 110–115 °C; Table 2). The optical activities of all the new CD derivatives were measured in chloroform solution (Table 1). The cation and the anion in all CD ILs were identified by electrospray ionization (ESI) high-resolution mass spectrometry (Table 3). The CD-pyridinium cation **4a** and **4b**, and the CD-imidazolium cation **5a** and **5b** were recorded in the positive mode, and the negative ionization mode was used to record the mass spectra of anionic moieties of CD ILs, the singly charged anion [$CF_3SO_3^-$].

Table 3. High-resolution mass spectrometry data of CD ILs **4a**,**b** and **5a**,**b**.

Compound	MS positive analysis found/ *calcd for [cation]*	MS negative analysis found/ *calcd for [$CF_3SO_3^-$]*
4a	1272.6186/*1272.6219*	148.9523/*148.9526*
4b	1476.7219/*1476.7217*	148.9530/*148.9526*
5a	1287.6322/*1287.6328*	148.9526/*148.9526*
5b	1491.7256/*1491.7326*	148.9529/*148.9526*

The MALDI-TOF spectrum of **4a**, acquired from m/z = 500–2000 Da, displays the cluster m/z = 1272.5670–1276.5570 Da, which corresponds to the molecular cation, in a purity of 92.6% (calculated from the areas of the mass peaks, see the Supporting Information). Considering that the matrix effect, cluster m/z = 1424.5673–1426.5763 Da, resulting from the inclusion of 2,5-dihydroxybenzoic acid (DHB, molar mass = 154.0266 Da) in the CD-based IL **4a**, is responsible for 3.1% of the peak area, the overall purity of **4a** used to coat the column was 95.7%. This achieved purity was considered enough to claim that the column was coated with a high-purity compound.

The thermal properties of the CD ILs **4** and **5** were evaluated through thermogravimetric (TG) and differential scanning calorimetry (DSC) analyses. Figure 1 depicts the TG curve (trace a) and DSC profile (trace b) of permethylated mono-6-deoxy-6-(pyridin-1-ium)-α-cyclodextrin trifluoromethanesulfonate (**4a**) on heating to 410 °C under nitrogen (7 °C min^{-1}). The onset of the endothermic event appearing at 274.9 °C (peaking at 278.2 °C) corresponds to the decomposition of the compound and is accompanied by about 46.5% weight losses by the end of transition. The residual mass at 410 °C is around 50%. The thermal behavior of CD ILs **4b** and **5a** were very similar, with the corresponding endothermic events at 270.8 °C (onset 267.7 °C) and 289.0 °C (onset 277.6 °C), respectively, whereas for **5b** a significantly lower decomposition temperature was registered (peak at 244.1 °C, onset at 215 °C). These events were accompanied by approximately 64.0, 61.9, and 34.0% weight loss by the end of the transitions, respectively. In general, CD ILs (**4a**, **4b**, **5a**) were found to be stable up to 250 °C, as indicated by the TG analysis measurements.

To explore the properties of chiral selectivity and thermal stability of the new chiral ILs (**4** and **5**) derived from α- (**4a** and **5a**) and β-CDs (**4b** and **5b**), mono-6-deoxy-6-pyridin-1-ium-α-cyclodextrin trifluoromethanesulfonate (**4a**) was used as stationary phase in enantio-GC. The salt of α-CD **4a** is a viscous room-temperature IL, so it could be used in its neat form as stationary phase to coat directly the silica tubing. A solution of **4a** in dichloromethane (0.18% w/v) was used to fill 13 meters of fused-silica capillary tubing and to obtain a stationary phase film thickness of 0.11 μm.[34]

Supercooling, or glass formation, is a common characteristic associated with many ILs.[35] Usually, imidazolium ILs exhibit glass transition temperatures below the melting point temperature. As reported,[36] the glass transition temperatures of some imidazolium ILs are between −104 and −75 °C, depending on the alkyl substituents in the imidazolium ring and on the nature of the anion, whereas the corresponding melting points are from −81 to 60 °C. Herein, a volatile solvent, dichloromethane, was used to dissolve the stationary phase **4a** during the column coating procedure and was evaporated at 40 °C and reduced pressure. Although this temperature is below the melting point of **4a**, it will be probably above its glass transition temperature, thus favoring an almost homogeneous deposition of the stationary phase during solvent evaporation. However, a higher evaporation temperature, superior to the **4a** melting point (>85 °C), should favor the homogeneity of deposition and thus provide better column efficiencies and separations.

The calculated efficiency at 120 °C for tetradecane was 330 theoretical plates per meter (k = 6.6, with k the retention factor $(t_r - t_0)/t_0$). The column efficiency is low, but nevertheless some interesting enantioseparations were achieved. Some compound chemical families

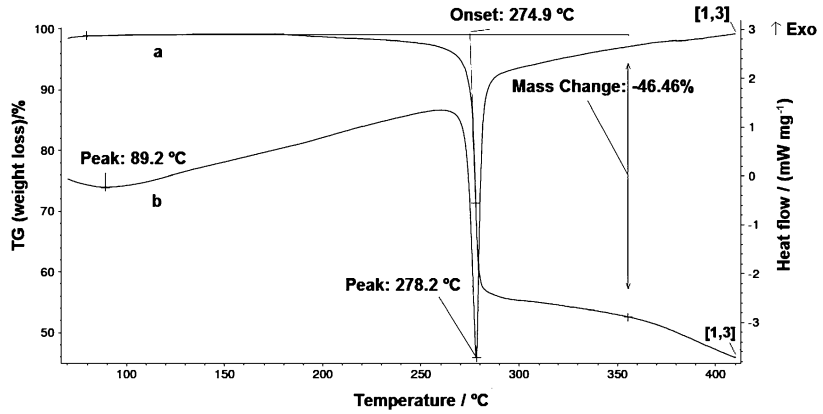
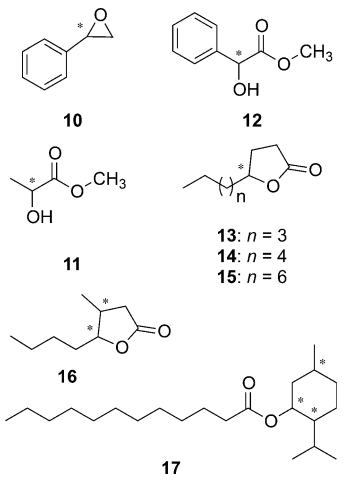


Figure 1. TG (a) and DSC (b) thermograms of CD-based IL **4a** measured in N_2 (heating rate 7 °C min^{-1}).

were separated successfully if enantiomeric mixtures were analyzed (Scheme 6). This problem is not new and has already been reported by Huang et al.[29] In fact, probably the smaller anion occupies the CD cavity, thereby reducing the inclusion



Scheme 6. Chiral compounds **10**–**17**.

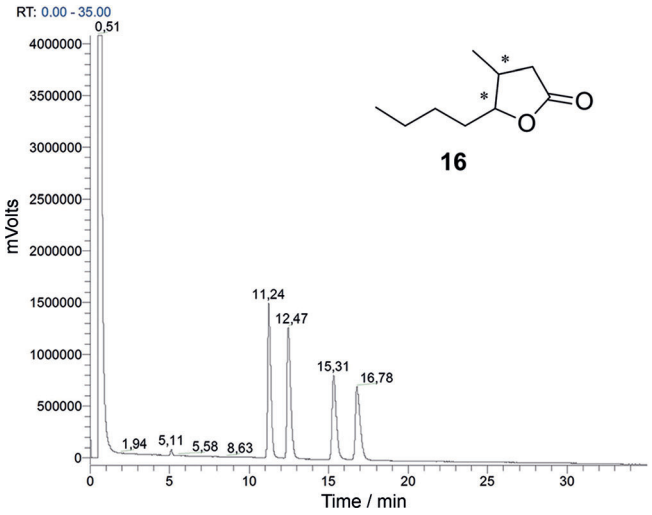


Figure 2. Separation of the four enantiomers of whiskey lactone (**16**) in a sample solution. The GC instrument was operated using a split/splitless injector set at 100 mL min^{-1}. The injector and FID were set at 250 °C. The carrier gas was hydrogen adjusted to give a solvent peak after around 0.50 min. A 1 μL portion of 150 ppm sample solution in hexane was injected. The GC oven was operated exothermically at 120 °C.

complexation interaction between the chiral phase and the target analyte. On the other hand, the chiral selector **4a** displays good enantiomeric separation for some esters and lactones, as well as epoxides (Table 4). In the particular case of racemic menthyl laurate **17** (Scheme 6), the enantiomeric separation was achieved isothermally at 140 °C despite its high boiling point. The same racemic mixture was not separated successfully in a commercial CD phase at 210 °C.

Table 4. Enantioseparation of eight compounds (**10**–**17**) in a GC column of permethylated mono-6-deoxy-6-(pyridin-1-ium)-α-cyclodextrin trifluoromethanesulfonate (**4a**) stationary phase. Summary of the chromatographic parameters.

Compound	T [°C]	$k'1$	$k'2$	$\alpha 1$	Rs_1	N m^{-1}
10	120	5.14	5.43	1.06	0.27	353
11	130	3.75	3.86	1.03	0.10	13
12	140	8.63	9.04	1.05	0.30	1342
13	140	10.79	10.92	1.01	0.13	25
14	140	21.44	22.08	1.03	0.19	52
15	140	54.94	55.49	1.01	0.03	13
16[a]	120	21.04	23.45	1.11	1.50	1227
17	140	210.13	216.23	1.03	1.01	2819

[a] $k'3 = 29.02$ and $k'4 = 31.90$, $\alpha 2 = 1.10$ and $Rs_2 = 1.79$.

The thermal stability of the phase was tested up to 160 °C, at which no significant bleeding was observed. A temperature program run from 40 to 160 °C (held overnight, 16 h) did not result in an enhanced flame ionization detector (FID) response. The chromatographic parameters and the enantioseparation for the whiskey lactone **16** (four diastereoisomers) were kept constant at 120 °C after submitting the column to 160 °C overnight, 16 h (Figure 2).

The column phase showed selectivity for some organic compound families, such as epoxides **10** (ethers) and hydroxy esters **11** and **12**, lactones **13**–**16**, and in particular a heavy ester **17**. Other compound families, such as hydrocarbons, ketones, carboxylic acids, amines, and amides, were also assayed, but no enantioselectivity was observed. Menthyl laurate (**17**) racemic mixture was separated successfully at 140 °C in this stationary phase, which was not achieved if a commercial CD column (CyclodexB, J&W, 30 m × 0.25 mm, 0.25 μm) was used. In this commercial phase, after an isothermic run of 4 hours at 210 °C, no elution occurred. This is quite remarkable, since menthyl laurate (**17**) is a heavy molecular mass compound, with low volatility.

Conclusion

In summary, we have synthesized the first room-temperature ionic liquids (ILs) derived from α- and β-cyclodextrins (CDs), the permethylated mono-6-deoxy-6-piridin-1-ium and mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium) α-CD and β-CD trifluoromethanesulfonates at room temperature in a solvent-free procedure. Mono-6-deoxy-6-pyridin-1-ium-α-cyclodextrin trifluoromethanesulfonate (**4a**) was used as stationary phase in enantio-GC and epoxides **10** (ethers) and hydroxy esters **11** and **12**, and lactones **13**–**16** in racemic mixtures were separated successfully. Both enantiomers of (±)-menthyl laurate (**17**) were discriminated at 140 °C in this stationary phase, which was not achieved if a commercial CD column was used. Further, the synthesis of CD room-temperature ILs to be used as stationary phases in enantio-GC is now under investigation.

Experimental Section

General methods and instrumentation

Thin-layer chromatography (TLC) was performed on silica gel plates (60 F254, Merck, ref. 1.05554) and visualized either by spraying with sulfuric acid/methanol (1:1) followed by heating at 120 °C or with iodine vapor. Silica gel (230–400 mesh ASTM, Merck) was used for flash chromatography. α- and β-cyclodextrins (CDs) were dried overnight 20 h under vacuum over P_2O_5 at 100 °C. Imidazole was dried overnight, 20 h under vacuum over P_2O_5 at room temperature. Methanol was dried with sodium and distilled. Dimethylformamide, pyridine, dichloromethane, and 1-vinylimidazole were dried over 4 Å molecular sieves previously ignited 30 min at 300 °C. All remaining materials were used without additional purification.

The IR spectra were recorded in a PerkinElmer Spectrum 1000 spectrometer. ^{1}H NMR (400.13 MHz), ^{13}C NMR (100.61 MHz), ^{1}H–^{1}H correlation spectroscopy (COSY), ^{13}C–^{1}H heteronuclear single quantum correlation (HSQC), heteronuclear multiple bond correlation (HMBC), and ^{19}F NMR (376 MHz) spectra were recorded in a suitable solvent by using a Bruker ARX 400 spectrometer. The splitting parameters for ^{1}H NMR spectroscopy are denoted as follows: s (singlet), d (doublet), t (triplet), and m (multiplet). Spectra were obtained in $CDCl_3$ containing a trace of TMS ($\delta = 0$ ppm) as the internal standard, using a δ (ppm) scale. High-resolution mass spectra (ESI-TOF) were obtained at the RIAIDT of Universidad de Santiago de Compostela and measured on a Bruker Amazon ETD (micrOTOF) instrument. MALDI-TOF measurements were performed at Laboratório de Analises/Requimte of the Universidade Nova de Lisboa and measured on a Voyager-DETM PRO workstation, in positive mode using a DHB matrix. Optical rotations were recorded in a PerkinElmer 241 MC polarimeter.

Thermogravimetric (TG) and differential scanning calorimetry (DSC) analyses were performed on a Netzsch Luxx STA 409 PC, at a heating rate of 7 °C min^{-1} under nitrogen from 60 to 410 °C at the Centro de Investigação de Engenharia Química e Biotecnologia, Instituto Superior de Engenharia, Portugal. The analytical tests were performed in a GC Trace instrument (Thermo Finnigan, USA) equipped with a split/splitless injector and a flame ionization detector (FID), both set at 250 °C. The carrier gas was hydrogen, at 45 kPa. A sample volume (1 μL) was injected at a split flow of 150 mL min^{-1}. The chromatograms were processed by using the automated data processing software Xcalibur from Thermo Finnigan (ThermoFinnigan, Austin, TX, USA).

Synthesis of permethylated mono-6-trifluoromethanesulfonate-β-cyclodextrin (9b)

Trifluoromethanesulfonic anhydride (0.198 g, 0.70 mmol) was added dropwise to a cold stirred solution of **8b** (72.4 mg, 0.051 mmol) in dry 1-vinylimidazole (1 mL). The reaction mixture was allowed to warm to room temperature and stirred for 2 days. TLC (EtOAc/CH_3OH 10:1) showed the formation of two new compounds, one at $R_f = 0$ and the other with higher R_f than **8b**. The solution was cooled to 0 °C, diluted with cold CH_2Cl_2 (10 mL), washed with cold aqueous HCl 5% (2×5 mL), cold aqueous $NaHCO_3$ 5% (5 mL), and cold water (2 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by column chromatography on silica gel ($CHCl_3$/CH_3OH 10:2) to give pure **9b** (29.8 mg, 37.6%) as an oil.

Data for permethylated mono-6-trifluoromethanesulfonate-β-cyclodextrin (9b)

^{1}H NMR ($CDCl_3$): $\delta = 5.30$–5.07 (m, 7H; 6×H-1′ and H-1), 4.66 (dd, $J = 17.8$, 8.0 Hz, 1H; H-6), 4.56 (m, 1H; H-6), 4.00 (m, 1H; H-5), 3.95–3.37 (m, 92H; 6×H-3′, 6×H-4′, 6×H-5′, H-3, H-4, 12×H-6′, 20×OCH_3), 3.19 (dd, $J = 9.6$, 3.0 Hz, 6H; 6×H-2′), 3.14 ppm (dd, $J = 9.7$, 3.4 Hz, 1H; H-2); ^{13}C NMR ($CDCl_3$): $\delta = 99.61$ (C-1′ or C-1), 99.56 (C-1′ or C-1), 99.48 (C-1′ or C-1), 99.38 (C-1′ or C-1), 99.13 (C-1′ or C-1), 99.09 (C-1′ or C-1), 99.02 (C-1′ or C-1), 82.16, 82.12, 82.01, 81.91, 81.87, 81.83, 81.56, 81.47, 80.85, 80.75, 80.53, 80.46, 80.44, 80.41, 80.31, 80.12, 71.61 (C-6′), 71.58 (C-6′), 71.50 (C-6′), 71.45 (C-6′), 71.43 (C-6′), 71.40, 71.36, 71.32 (C-6′), 71.16, 71.12, 71.02, 68.56 (C-6), 61.70, 61.69, 61.66, 61.61, 61.54, 61.46, 61.42, 59.17, 59.10, 59.06, 58.95, 58.84, 58.77, 58.65, 58.59, 58.55 ppm; FTIR (film): $\tilde{\nu} = 2929$ (C-H), 2834 (C-H), 1455 (S=O), 1195, 1039, 972 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{63}H_{111}F_3O_{37}S^+$: 1548.6472 [$M + 2H^+$]; found: 1548.6467.

Synthesis of permethylated mono-6-deoxy-6-(pyridin-1-ium)-α-cyclodextrin trifluoromethanesulfonate (4a)

In dichloromethane: Trifluoromethanesulfonic anhydride (0.018 mL, 30 mg, 0.107 mmol) was added dropwise to a cool solution of **8a** (75 mg, 0.062 mmol) in dry pyridine (0.15 mL, 147.3 mg, 1.86 mmol) in dry dichloromethane (1 mL). The reaction mixture was stirred for 7 days at room temperature under argon. TLC (chloroform/methanol 10:1) showed that all starting material was consumed and a new lower spot (R_f 0.11) was formed. The solution was cooled to 0 °C, diluted with dichloromethane (10 mL), washed with aqueous HCl 5% (5 mL), aqueous $NaHCO_3$ 5% (5 mL), and water (2 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give **4a** (57 mg). Chromatography on silica gel with chloroform/methanol (10:1) as eluent afforded pure **4a** as a solid (29.6 mg, 0.021 mmol, 33.9%).

Without solvent: A solution of **8a** (100.7 mg, 0.083 mmol) in dry pyridine (2 mL) was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.07 mL, 117.4 mg, 0.416 mmol) was added dropwise. The reaction was stirred for 2 days at room temperature under argon. TLC (chloroform/methanol 10:1) showed that all starting material was consumed and a new lower spot (R_f 0.11) was formed. The solution was cooled to 0 °C, diluted with dichloromethane (70 mL), washed with aqueous HCl 5% (2×10 mL), aqueous $NaHCO_3$ 5% (2×10 mL), and water (2×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give **4a**. Chromatography on silica gel with chloroform/methanol (9:1) as eluent afforded pure **4a** (75.1 mg, 0.059 mmol, 71.1%) as a solid.

Data for permethylated mono-6-deoxy-6-(pyridin-1-ium)-α-cyclodextrin trifluoromethanesulfonate (4a)

M.p. 84–85 °C; $[\alpha]_D^{21} = +126.8$ ($c = 3.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 9.05$ (d, $J = 5.8$ Hz, 2H; H-2″, H-6″), 8.54 (t, $J = 7.8$ Hz, 1H; H-4″), 8.05 (m, 2H; H-3″, H-5″), 5.30 (dd, $J = 14.3$, 2.7 Hz, 1H; H-6), 5.19 (dd, $J = 14.6$, 3.7 Hz, 1H; H-6), 5.13 (d, $J = 3.1$ Hz, 1H; H-1), 5.07 (m, 3H; 3×H-1′), 4.97 (d, $J = 3.3$ Hz, 1H; H-1′), 4.92 (d, $J = 3.5$ Hz, 1H; H-1′), 4.39–2.82 ppm (m, 85H; H-2, H-3, H-4, H-5, 5×H-2′, 5×H-3′, 5×H-4′, 5×H-5′, 10×H-6′, 17×OCH_3); ^{13}C NMR ($CDCl_3$): $\delta = 146.72$ (C-2″, C-6″), 145.77 (C-4″), 127.95 (C-3″, C-5″), 100.54 (C-1′), 100.44 (C-1′), 100.26 (C-1′), 100.20 (C-1′), 99.41 (C-1), 83.63, 82.52, 82.47, 82.43, 82.34, 82.26, 82.21, 82.14, 82.08, 81.95, 81.91, 81.56, 81.41, 81.36, 81.22, 81.12, 80.90, 72.34 (C-6′), 72.18, 71.60, 71.47 (C-6′), 71.28 (C-6′), 71.15, 69.41, 62.12, 62.00, 61.94, 61.86, 61.8, 61.78,

61.09 (C-6), 59.74, 59.27, 59.21, 59.15, 59.07, 58.78, 58.26, 58.11, 58.10, 57.99, 57.90 ppm; ^{19}F NMR ($CDCl_3$): $\delta = -78.34$ ppm (s, $CF_3SO_3^-$); FTIR (KBr): $\tilde{\nu} = 2926$, 2858, 1458, 1261, 1162, 1110, 1041 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{58}H_{98}NO_{29}^+$: 1272.6219 [*cation*]; found: 1272.6186; *m/z* calcd for $CF_3SO_3^-$: 148.9526 [*anion*]; found: 148.9523.

Data for permethylated mono-6-deoxy-6-(pyridin-1-ium)-β-cyclodextrin trifluoromethanesulfonate (4 b)

$\eta = 38.2\%$; m.p. 110–115 °C; $[\alpha]_D^{21} = +91.6$ ($c = 1.4$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 9.11$ (d, $J = 4.4$ Hz, 2H; H-2″ and H-5″), 8.54 (t, $J = 7.0$ Hz, 1H; H-4″), 8.06 (m, 2H; H-2″ and H-4″), 5.35 (d, $J = 12.8$ Hz, 1H; H-6), 5.17 (d, $J = 3.32$ Hz, 1H; H-1′), 5.12 (m, 3H; H-6, 2×H-1′), 5.09 (d, $J = 3.11$ Hz, 1H; H-1′), 5.06 (d, $J = 3.44$, 1H; H-1′), 5.00 (d, $J = 3.42$ Hz, 1H; H-1′), 4.29 (d, $J = 8.8$ Hz, 1H; H-5), 4.07–2.92 (m, 99H; H-3, H-4, H-5, 6×H-2′, 6×H-3′, 6×H-4′, 6×H-5′, 12×H-6′, 20×OCH_3), 2.94 ppm (dd, $J = 2.27$, 9.62 Hz, 1H; H-2); ^{13}C NMR ($CDCl_3$): $\delta = 146.84$ (C-2″, C-6″), 145.75 (C-4″), 127.79 (C-3″, C-5″), 100.38 (C-1′), 100.07 (C-1′), 99.35 (C-1′), 99.27 (C-1′), 99.12 (C-1′), 98.04 (C-1), 82.27, 82.19, 82.22, 82.12, 82.07, 81.96, 81.86, 81.81, 81.77, 81.58, 81.47, 81.34, 81.00, 80.82, 80.75, 80.42, 80.11, 79.81, 72.76 (C-6′), 71.76, 71.71 (C-6′), 71.44 (C-6′), 71.39 (C-6′), 71.29, 71.13, 71.08, 70.98, 69.28, 61.77, 61.63, 61.58, 61.53, 61.46, 61.36, 61.27, 61.19 (C-6), 59.75, 59.40, 59.33, 59.17, 59.13, 59.08, 58.84, 58.72, 58.61, 58.46, 58.43 ppm; ^{19}F NMR ($CDCl_3$): $\delta = -78.00$ ppm (s, CF_3); FTIR (KBr): $\tilde{\nu} = 2930$, 2834, 1461, 1455, 1262, 1162, 1108, 1033, 639 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{67}H_{114}NO_{34}^+$: 1476.7217 [*cation*]: found: 1476.7219; *m/z* calcd for $CF_3SO_3^-$:148.9526 [*anion*]; found: 148.9530.

Synthesis of permethylated mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-α-cyclodextrin trifluoromethanesulfonate (5 a)

A solution of **8 a** (108.2 mg, 0.089 mmol) in dry 1-vinylimidazole (2 mL) was stirred and cooled to 0 °C under an argon atmosphere. Then trifluoromethanesulfonic anhydride (1.03 mL, 1.727 g, 6.12 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 19 h. TLC (EtOAc/CH_3OH 10:1) showed the formation of two new spots, one at the baseline and the other with higher R_f. The solution was cooled again (0 °C), diluted with cold CH_2Cl_2 (10 mL), washed with cold HCl 5% (2×5 mL), cold aqueous $NaHCO_3$ 5% (5 mL), and cold water (2 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. The product obtained was subjected to column chromatography on a silica gel with $CHCl_3/CH_3OH$ (10:2) as eluent to give pure **5 a** (73.5 mg, 67.2%).

Data for permethylated mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-α-cyclodextrin trifluoromethanesulfonate (5 a)

$\eta = 41.5\%$; m.p. 95–100 °C; $[\alpha]_D^{21} = +119.0$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 9.27$ (s, 1H; H-2″), 7.74 (s, 1H; H-5″), 7.57 (s, 1H; H-4″), 7.34 (dd, $J = 15.5$, 8.6 Hz, 1H; H-6″), 5.77 (dd, $J = 15.6$, 2.9 Hz, 1H; H-7″*trans*), 5.46 (dd, $J = 8.6$, 2.9 Hz, 1H; H-7″*cis*), 5.18 (d, $J = 3.0$ Hz, 1H; H-1), 5.12–5.02 (m, 3H; 3×H-1′), 4.99–4.84 (m, 3H; H-6, 2×H-1′), 4.67 (d, $J = 12.6$ Hz, 1H; H-6), 4.16–3.29 (m, 79H; H-3, H-4, H-5, 5×H-3′, 5×H-4′, 5×H-5′, 10×H-6′, 17×OCH_3), 3.24–3.11 ppm (m, 6H; H-2, 5×H-2′); ^{13}C NMR ($CDCl_3$): $\delta = 131.05$ (C-2″), 128.82 (C-6″), 124.76 (C-5″), 118.18 (C-4″), 110.41 (C-7″), 100.66 (C-1′), 100.48 (C-1′), 100.36 (C-1′), 100.30 (C-1′), 100.27 (C-1′), 99.40 (C-1), 83.76, 82.58, 82.51, 82.39, 82.27, 82.16, 82.00, 81.55, 81.39, 81.36, 81.22, 81.01, 72.51 (C-6′), 72.06 (C-6′), 71.59, 71.47 (C-6′), 71.41, 71.37, 68.72, 62.14, 62.00, 61.96, 61.84, 59.86, 59.29, 59.23, 59.19, 59.13, 58.75, 58.21, 58.11, 58.04, 58.02, 57.94, 50.51 ppm (C-6); ^{19}F NMR ($CDCl_3$): $\delta = 78.47$ (s, CF_3); FTIR (film): $\tilde{\nu} = 2930$, 2834, 1667, 1454, 1262, 1162, 1037, 639 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{58}H_{99}N_2O_{29}^+$: 1287.6328 [*cation*]; found: 1287.6322; *m/z* calcd for $CF_3SO_3^-$: 148.9526 [*anion*]; found: 148.9526.

Data for permethylated mono-6-deoxy-6-(1-vinyl-1*H*-imidazol-3-ium)-β-cyclodextrin trifluoromethanesulfonate (5 b)

$\eta = 29.5\%$; m.p. 95–99 °C; $[\alpha]_D^{21} = +117.1$ ($c = 0.92$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 9.44$ (s, 1H; H-2″), 7.80 (s, 1H; H-5″), 7.55 (s, 1H; H-4″), 7.34 (dd, $J = 15.5$, 8.6 Hz, 1H; H-6″), 5.76 (dd, $J = 15.6$, 2.8 Hz 1H; H-7″*trans*), 5.45 (dd, $J = 8.6$, 2.7 Hz, 1H; H-7″*cis*), 5.17 (d, $J = 3.4$ Hz, 2H; 2×H-1′), 5.15–5.10 (m, 2H; 2×H-1′), 5.08 (d, $J = 3.3$ Hz, 1H; H-1′), 4.98 (d, $J = 3.7$ Hz, 2H; H-1, H-1′), 4.84 (dd, $J = 14.6$, 2.8 Hz, 1H; H-6), 4.61 (dd, $J = 2.3$, 14.4 Hz, 1H; H-6), 4.20–2.96 ppm (m, 100H; H-2, H-3, H-4, H-5, 6×H-2′, 6×H-3′, 6×H-4′, 6×H-5′, 12×H-6′, 20×OCH_3); ^{13}C NMR ($CDCl_3$): $\delta = 137.53$ (C-2″), 128.86 (C-6″), 124.86 (C-5″), 118.18 (C-4″), 110.13 (C-7″), 100.41 (C-1′), 100.32 (C-1′), 99.27 (C-1′), 99.18 (C-1′), 98.07 (C-1), 82.53, 82.34, 82.23, 82.13, 81.85, 81.79, 81.62, 81.43, 81.22, 80.99, 80.78, 80.59, 80.00, 72.81 (C-6′), 71.90 (C-6′), 71.61, 71.49 (C-6′), 71.42, 71.37, 71.31, 71.16 (C-6′), 71.04, 68.54, 61.79, 61.59, 61.52, 61.43, 61.23, 59.83, 59.34, 59.17, 59.15, 59.09, 59.08, 58.98, 58.71, 58.48, 58.45, 58.40, 50.35 ppm (C-6); ^{19}F NMR ($CDCl_3$): $\delta = -78.42$ ppm (s, $CF_3SO_3^-$); FTIR (film): $\tilde{\nu} = 2930$ (C-H), 2833 (C-H), 1458, 1262, 1162, 1032, 639 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{67}H_{115}N_2O_{34}^+$: 1491.7326 [*cation*]; found: 1491.7256; *m/z* calcd for $C_{67}H_{115}N_2NaO_{34}^{2+}$: 757.3609 [*cation* + Na^+]; found 757.3601; *m/z* calcd for $CF_3SO_3^-$: 148.9526 [*anion*]; found: 148.9529.

GC column coating

Untreated fused-silica capillary tubing (250 μm i.d.) was purchased from SGE Analytical Science, Ringwood, Victoria, Australia; 13 m of capillary tubing were used to prepare the column. Before coating, the untreated fused-silica capillary tubing was rinsed with acetone P.A. (2.6 mL, corresponding to four times the volume of the 13 m coil). To remove the washing solvent, the coil was purged with a stream of nitrogen for 15 min. To prepare the coating solution, permethylated mono-6-deoxy-6-(pyridin-1-ium)-α-cyclodextrin trifluoromethanesulfonate (**4 a**; 18 mg) was dissolved in dichloromethane P.A. (10 mL) to obtain a solution concentration of 0.18% (w/v). Considering the diameter of the capillary tubing (250 μm i.d.) and the percentage by weight concentration of the stationary phase dissolved in dichloromethane, the estimated film thickness was 0.11 μm.[18b,34] One end was sealed with an epoxy glue (Ceys Araldit) and maintained 2 days at controlled ambient temperature and humidity to dry. The filled coil was then submitted to 5.5 bar pressure (helium) during 4 days to remove any air bubbles, which could cripple the subsequent solvent evaporation step. The evaporation process took place in a water bath at 40 °C under a reduced pressure of 7 mm Hg. After 2 days, the solvent was evaporated and the filled column was submitted to a helium flow for 2 h (under a pressure of 0.5 bar) and then conditioned from 50 to 120 °C at 1 °C min^{-1}. This temperature was held overnight 20 h. The efficiency of the coated column was tested with a standard solution of tetradecane in dichloromethane at 120 °C. The calculated retention factor (*k*) was 6.6. The calculated number of plates per meter of column was 330. All further analyses were performed under the same instrument conditions (see above for details).

Acknowledgements

This study was supported by the Fundação para a Ciência e Tecnologia (FCT, Portugal) through PTDC/QUI-QUI/100672/2008. The NMR spectrometers are part of The National NMR Facility, supported by FCT (RECI/BBB-BQB/0230/2012).

Keywords: cyclodextrins · enantioselectivity · gas chromatography · ionic liquids · regioselectivity

[1] J. Huang, X. Zhang, D. W. Armstrong, *Angew. Chem.* **2007**, *119*, 9231 – 9235; *Angew. Chem. Int. Ed.* **2007**, *46*, 9073 – 9077.
[2] a) L. Marinescu, M. Bols, *Curr. Org. Chem.* **2010**, *14*, 1380 – 1398; b) S. Y. Chen, X. T. Zhou, H. B. Hu, *Chin. J. Org. Chem.* **2012**, *32*, 686 – 695; c) Y. S. Fung, S. C. Yan, M. K. Wong, *Org. Biomol. Chem.* **2012**, *10*, 3122 – 3130.
[3] a) L. Boffa, E. C. Gaudino, K. Martina, L. Jicsinszky, G. Cravotto, *New J. Chem.* **2010**, *34*, 2013 – 2019; b) H. M. Shen, H. B. Ji, *Chin. J. Org. Chem.* **2011**, *31*, 791 – 803; c) G. H. C. Varca, N. Andreo, P. S. Lopes, H. G. Ferraz, *Curr. Protein Pept. Sci.* **2010**, *11*, 255 – 263; d) W. Zhao, Q. Zhong, *J. Inclusion Phenom. Macrocyclic Chem.* **2012**, *72*, 1 – 14.
[4] D. W. Armstrong, W. DeMond, *J. Chromatogr. Sci.* **1984**, *22*, 411 – 415.
[5] P. Zhang, A. X. Wang, L. N. Cui, C. C. Ling, *Org. Lett.* **2012**, *14*, 1612 – 1615.
[6] a) V. T. D'Souza, K. B. Lipkowitz, *Chem. Rev.* **1998**, *98*, 1741 – 1742; b) Y. Chen, Y. Liu, *Chem. Soc. Rev.* **2010**, *39*, 495 – 505; c) A. Harada, Y. Takashima, H. Yamaguchi, *Chem. Soc. Rev.* **2009**, *38*, 875 – 882; d) F. Bellia, D. La Mendola, C. Pedone, E. Rizzarelli, M. Saviano, G. Vecchio, *Chem. Soc. Rev.* **2009**, *38*, 2756 – 2781.
[7] Z. Chen, J. S. Bradshaw, M. L. Lee, *Tetrahedron Lett.* **1996**, *37*, 6831 – 6834.
[8] X. P. Zhang, C. Y. Zhang, G. L. Sun, X. D. Xu, Y. F. Tan, H. F. Wu, R. N. Cao, J. Liu, J. W. Wu, *Instrum. Sci. Technol.* **2012**, *40*, 194 – 215.
[9] a) D. W. Armstrong, T. J. Ward, R. D. Armstrong, T. E. Beesley, *Science* **1986**, *232*, 1132 – 1135; b) H. Dodziuk, W. Kozminski, A. Ejchart, *Chirality* **2004**, *16*, 90 – 105.
[10] a) R. Berkecz, I. Ilisz, A. Ivanov-Sztojkov, I. Szatmari, F. Fulop, D. W. Armstrong, A. Peter, *Chromatographia* **2007**, *65*, 337 – 341; b) C. Mitchell, M. Desai, R. McCulla, W. Jenks, D. Armstrong, *Chromatographia* **2002**, *56*, 127 – 135; c) X. Han, Q. Zhong, D. Yue, N. Della Ca, R. C. Larock, D. W. Armstrong, *Chromatographia* **2005**, *61*, 205 – 211; d) P. Sun, C. Wang, D. W. Armstrong, A. Peter, E. Forro, *J. Liq. Chromatogr. Relat. Technol.* **2006**, *29*, 1847 – 1860; e) Y. Tang, J. Zukowski, D. W. Armstrong, *J. Chromatogr. A* **1996**, *743*, 261 – 271.
[11] a) W. Keim, A. Köhnes, W. H. Meltzow, *J. High Resolut. Chromatogr.* **1991**, *14*, 507 – 529; b) A. Berthod, W. Y. Li, D. W. Armstrong, *Carbohydr. Res.* **1990**, *201*, 175 – 184; c) W. Y. Li, H. L. Jin, D. W. Armstrong, *J. Chromatogr.* **1990**, *509*, 303 – 324; d) W. A. König, S. Lutz, P. Mischnick-Lubbecke, B. Brassat, G. Wenz, *J. Chromatogr.* **1988**, *447*, 193 – 197; e) V. Schurig, H. P. Nowotny, *J. Chromatogr.* **1988**, *441*, 155 – 163; f) T. Koscielski, D. Sybilska, J. Jurczak, *J. Chromatogr.* **1983**, *280*, 131 – 134; g) D. W. Armstrong, W. Y. Li, C. D. Chang, J. Pitha, *Anal. Chem.* **1990**, *62*, 914 – 923; h) R. Q. Wang, T. T. Ong, W. H. Tang, S. C. Ng, *Anal. Chim. Acta* **2012**, *718*, 121 – 129; i) Y. Xiao, S.-C Ng, T. T. Y. Tan, Y. Wang, *J. Chromatogr. A* **2012**, *1269*, 52 – 68.; j) T. Chaise, P. Cardinael, S. Tisse, J. C. Combret, J. P. Bouillon, *Tetrahedron: Asymmetry* **2008**, *19*, 348 – 357.
[12] N. Jain, A. Kumar, S. Chauhan, S. M. S. Chauhan, *Tetrahedron* **2005**, *61*, 1015 – 1060.
[13] C. Ragonese, D. Sciarrone, P. Q. Tranchida, P. Dugo, L. Mondello, *J. Chromatogr. A* **2012**, *1255*, 130 – 144.
[14] a) D. W. Armstrong, L. F. He, Y. S. Liu, *Anal. Chem.* **1999**, *71*, 3873 – 3876; b) M. Koel, *Crit. Rev. Anal. Chem.* **2005**, *35*, 177 – 192.
[15] S. Sowmiah, V. Srinivasadesikan, M. C. Tseng, Y. H. Chu, *Molecules* **2009**, *14*, 3780 – 3813.
[16] Q. H. Zhang, S. G. Zhang, Y. Q. Deng, *Green Chem.* **2011**, *13*, 2619 – 2637.
[17] a) J. V. Seeley, S. K. Seeley, E. K. Libby, Z. S. Breitbach, D. W. Armstrong, *Anal. Bioanal. Chem.* **2008**, *390*, 323 – 332; b) A. Berthod, M. Ruiz-Ángel, S. Carda-Broch, *J. Chromatogr. A* **2008**, *1184*, 6 – 18; c) B. Buszewski, S. Studzinska, *Chromatographia* **2008**, *68*, 1 – 10; d) K. Huang, X. Han, X. Zhang, D. W. Armstrong, *Anal. Bioanal. Chem.* **2007**, *389*, 2265 – 2275; e) J. G. Huddleston, H. D. Willauer, R. P. Swatloski, A. E. Visser, R. D. Rogers, *Chem. Commun.* **1998**, 1765 – 1766; f) X. Han, D. W. Armstrong, *Acc. Chem. Res.* **2007**, *40*, 1079 – 1086; g) J. L. Anderson, D. W. Armstrong, G. T. Wei, *Anal. Chem.* **2006**, *78*, 2892 – 2902; h) C. Yao, J. L. Anderson, *Anal. Bioanal. Chem.* **2009**, *395*, 1491 – 1502.
[18] a) J. L. Anderson, D. W. Armstrong, *Anal. Chem.* **2003**, *75*, 4851 – 4858; b) J. L. Anderson, D. W. Armstrong, *Anal. Chem.* **2005**, *77*, 6453 – 6462; c) M. H. Abraham, C. F. Poole, S. K. Poole, *J. Chromatogr. A* **1999**, *842*, 79 – 114; d) Y. Wang, M. L. Tian, W. T. Bi, K. H. Row, *Int. J. Mol. Sci.* **2009**, *10*, 2591 – 2610.
[19] T. Payagala, D. W. Armstrong, *Chirality* **2012**, *24*, 17 – 53.
[20] N. V. Ignat'ev, P. Barthen, A. Kucheryna, H. Willner, P. Sartori, *Molecules* **2012**, *17*, 5319 – 5338.
[21] M. M. A. Pereira, *Mini-Rev. Org. Chem.* **2012**, *9*, 243 – 260.
[22] S. Kumar, U. Ramachandran, *Tetrahedron* **2005**, *61*, 4141 – 4148.
[23] W. H. Tang, J. Tang, S. C. Ng, H. S. O. Chan, *J. Inclusion Phenom. Macrocyclic Chem.* **2006**, *56*, 287 – 290.
[24] V. Tamara Perchyonok, *Curr. Org. Chem.* **2011**, *15*, 3120 – 3125.
[25] a) J. Y. Huang, M. Lei, Y. G. Wang, *Tetrahedron Lett.* **2006**, *47*, 3047 – 3050; b) C. K. Yerneni, V. Pathak, A. K. Pathak, *J. Org. Chem.* **2009**, *74*, 6307 – 6310.
[26] a) W. M. Tang, I. Wayan, *Tetrahedron: Asymmetry* **2007**, *18*, 1548 – 1553; b) R.-Q. Wang, T.-T. Ong, S.-C. Ng, *J. Chromatogr. A* **2008**, *1203*, 185 – 192.
[27] T.-T. Ong, R.-Q. Wang, I. W. Muderawan, S.-C. Ng, *J. Chromatogr. A* **2008**, *1182*, 136 – 140.
[28] J. Ding, T. Welton, D. W. Armstrong, *Anal. Chem.* **2004**, *76*, 6819 – 6822.
[29] K. Huang, X. T. Zhang, D. W. Armstrong, *J. Chromatogr. A* **2010**, *1217*, 5261 – 5273.
[30] N. Lupescu, C. K. Y. Ho, G. C. Jia, J. J. Krepinsky, *J. Carbohydr. Chem.* **1999**, *18*, 99 – 104.
[31] a) N. Zhong, H. S. Byun, R. Bittman, *Tetrahedron Lett.* **1998**, *39*, 2919 – 2920; b) T. F. Kaneda, Tatsuhiko, *Chem. Lett.* **2002**, 514.
[32] F.-X. Legrand, *New J. Chem.* **2011**, *35*, 2061 – 2065.
[33] A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.* **1998**, *98*, 1977 – 1996.
[34] J. González-Álvarez, D. Blanco-Gomis, P. Arias-Abrodo, D. Díaz-Llorente, N. Ríos-Lombardía, E. Busto, V. Gotor-Fernández, M. D. Gutiérrez-Álvarez, *Anal. Chim. Acta* **2012**, *721*, 173 – 181.
[35] S. A. Mirkhani, F. Gharagheizi, P. Ilani-Kashkouli, N. Farahani, *Thermochim. Acta* **2012**, *543*, 88 – 95.
[36] J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker, R. D. Rogers, *Green Chem.* **2001**, *3*, 156 – 164.
[37] T. Gubica, A. Pelka, K. Palka, A. Temeriusz, M. Kanska, *Carbohydr. Res.* **2011**, *346*, 1855 – 1859.
[38] G. B. Yi, S. Jerald, B. E. Rossiter, A. Malik, W. Li, M. L. Lee, *J. Org. Chem.* **1993**, *58*, 4844 – 4850.

Received: June 14, 2013
Revised: August 28, 2013
Published online on October 2, 2013