

Chiral pyrrolidinium salts derived from menthol as precursor – synthesis and properties

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Six new chiral pyrrolidinium salts with chiral substituent at quaternary nitrogen atom were synthesized with high overall yields from (-)-menthol as cheap chiral precursor and were identified by NMR and HRMS spectroscopy. It was shown that anion type had the effect on chemical shift of protons adjacent to quaternary nitrogen atom and physical properties of these salts. Salts with NTf_2 or NPF_2 were in a liquid state at room temperature and characterized with the highest thermal stability among others. Furthermore, chiral ionic liquid with NTf_2 anion was used as solvent in Diels-Alder reaction and gave higher yield and stereoselectivity than in ionic liquids with achiral cations. Synthesized chiral salts have the potential as chiral solvents in synthesis and auxiliaries in analytical methods to improve chiral recognition.

Keywords: pyrrolidinium chiral salts, chiral ionic liquids, menthol, Diels-Alder reaction.

INTRODUCTION

Over the last years, an interest in chiral salts with quaternary nitrogen atom has expanded due to wide variety of possible structures and utility. The great advantage is the possibility of incorporation of the chiral elements to the structure of the cation and/or anion and modification of the structure according to the requirements of the further application. Many of these salts have the properties of ionic liquids, which besides utility as efficient chiral catalysts in enantioselective organic synthesis^{1–3} can be also used as chiral solvents⁴. Moreover, chiral ionic liquids bear the potential of chiral discrimination capabilities in the various analytical and separation methods⁵, such as chromatography, electrophoresis^{6–7} and NMR spectroscopy^{9–12}.

Synthesis of chiral ionic liquids is primarily conducted from chiral precursors, which occurs naturally and are easily available in pure enantiomeric form. Cyclic structures with functional groups, such as terpenoids are particularly desired, due to special steric hindrances and opportunity to modification and incorporation to the structure of chiral salts^{10,13}. Citronellal¹⁴, α -pinene¹⁵, camphene and camphor sulfonic acid^{4,16}, carvone¹⁷ and terpenic alcohols^{18–21} are examples of such starting materials. Among many terpenic alcohols, menthol is the cheapest and widely available. It has three chiral centers and can occur in eight optical isomers. The naturally occurring form is (*1R,2S,5R*)-2-isopropyl-5-methylcyclohexanol, also known as (-)-menthol.

Our studies reveal new chiral ionic liquids with a chiral substituent, obtained from (-)-menthol, at nitrogen of pyrrolidinium cation. Additionally, salts designed by us have hydroxyl and ether functionality, which enhance polarity and solvation properties²². The aim of our studies was the synthesis, identification and determination of physicochemical properties of chiral pyrrolidinium salts with different anions.

Until now there are no data about chiral pyrrolidinium ionic liquids, containing chiral fragment, which was derived from menthol. So far an utilization of benzylamine and (+)-tartaric acid²³, D-mannitol²⁴, L-proline through

N-methyl-L-prolinol^{25, 26}, (*S*)-2-aminobutan-1-ol²⁷ or (*S*)-nicotine²⁸ for synthesis of chiral pyrrolidinium ionic liquids was reported.

EXPERIMENTAL

Material

(-)-Menthol (Aldrich, $\geq 99\%$), N-(2-hydroxyethyl)pyrrolidine (Fluka $\geq 97\%$), lithium bis(trifluoromethylsulfonyl)imide, LiNTf_2 (IoLiTec, 99%), potassium trifluoromethanesulfonate, KOTf (Aldrich, 98%), lithium bis(pentafluoroethylsulfonyl)imide, LiNPF_2 (Fluorochem), sodium tetrafluoroborate, NaBF_4 (Fluorochem, 98%), sodium hexafluorophosphate, NaPF_6 (Fluorochem, 98%) were used to the synthesis of chiral ionic liquids.

Analytical methods

Water content was determined by Karl-Fischer titration using 831 KF Coulometer (Metrohm).

Concentration of the proper metal (Na, K, Li) in the prepared salts was determined by inductively coupled plasma optical emission spectrometry (ICP-OES) with Perkin-Elmer Optima 5300 DV instrument. Solutions to analysis were prepared by microwave-oven digestion of samples (125 mg) with Suprapure nitric acid (3 ml) for 24 h and then dilution with deionized water to 25 ml. Standard solution of Na, K or Li (0.5, 0.75 and 1.0 mg/L) were used for calibration. Considering the weight of the sample and the volume of the reconstituted solution, the metal concentrations in the synthesized salts was denoted below 70 ppm.

¹H NMR and ¹³C NMR spectra were recorded on a BRUKER DPX-400 spectrometer and are reported in ppm from internal tetramethylsilane with CDCl_3 as solvent.

High-resolution mass spectra (HRMS) were recorded on a Maldi SYNAPT G2-S HDMS spectrometer from Waters. The measurements were performed in positive ionization mode. Sample was introduced through a standard electrospray ion source into instrument. Condition of single mass analysis were as follows: tolerance: 5.0

mDa/DBE: min = -1.5, max = 300.0; Number of isotope peaks used for i-FIT = 5.

EI spectra were recorded on Autospec Premier magnetic sector mass spectrometer (Waters) working at a resolving power of 8000. The samples were introduced via a heated direct insertion probe.

Optical rotation was measured with AUTOPOL IV (Rudolph Research Analytical) polarimeter for solutions in methanol ($c = 1\%$ (m/v) in MeOH) at 589 nm. Accuracy of measurement was $\pm 0.002^\circ$.

Thermogravimetric analyses were performed with a thermobalance TG 209 F1 Libra (Netzsch). Sample was loaded in Al_2O_3 crucible and heated from 25°C to 1000°C with the rate of 5 K/min, at the flow of air (25 ml/min) and nitrogen (purge gas, 10 ml/min). TGA temperature calibration was made using five calibration standards (indium, bismuth, zinc, aluminium and silver, each of purity $> 99.999\%$) in nitrogen atmosphere.

DSC curves for chiral salts were registered on Q100 Differential Scanning Calorimeter (TA Instruments), in aluminium crucible, within the temperature range of $-90^\circ\text{C} \div 120^\circ\text{C}$ at a constant heating/cooling rate of 10 K/min in the atmosphere of nitrogen. Physical transitions were observed and measured. Peak temperature and midpoint temperature (ISO 11357-1:2009) were determined for melting and glass transition respectively, based on two measurements. Indium and mercury were used as standards in calibration of temperature and heat of phase transformations.

Density was measured using DDM2911 Density Meter (Rudolph Research Analytical) with a mechanical oscillating U-tube method. The instrument was calibrated with deionized water. Measurements were performed for sample of 2.5 ml, in the range of temperature $20 \div 80^\circ\text{C}$, controlled via Peltier system.

Dynamic viscosity of the prepared ionic liquids was measured using Rheometer RC30-CPS equipped with cone-plate measuring system C50-1 (viscosity measuring range from 0.003 to 2500 Pa · s) and Peltier heating system (temperature range $0 \div 120^\circ\text{C}$). Measurements were carried out for 0.7 mL samples of ionic liquid in the range of temperature $20 \div 80^\circ\text{C}$, with increasing and decreasing shear rate in the range $0 \div 6000 \text{ s}^{-1}$. Rheometer was calibrated with GUM no. 2.17 (Polibuten PB-15) as standard. Standard deviation estimated for twelve measurements at specified temperature was $< 10^{-3} \text{ Pa} \cdot \text{s}$.

Refractive index was measured using Mettler Toledo Refracto 30 PX (accuracy ± 0.0005 ; resolution 0.0001) at room temperature (accuracy $\pm 0.2^\circ\text{C}$). The instrument was calibrated with water as the reference substance.

Synthesis of N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium chloride, [M(2HEt)pyrr][Cl]

In a round bottom flask, equipped with a magnetic stirring bar, was placed N-(2-hydroxyethyl)pyrrolidine (6.96 g; 0.060 mole) in 120 ml of anhydrous diethyl ether. The solution was stirred at 0°C and chloromethyl-(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl ether (12.68 g; 0.062 mole), prepared and purified according to procedure previously described¹⁹, was added drop by drop via syringe. The resulting slurry was stirred at 25°C for 24 h. White precipitate was then filtered and the filter

cake was washed three times with 20 ml of diethyl ether. Pure product was obtained by crystallization with diethyl ether/hexane mixture and drying in vacuum dryer at 40°C for 24 h. The yield of N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium chloride was 93% (17.8 g; 0.056 mole).

HRMS (TOF MS ES+): found 284.2591 (calculated for cation $\text{C}_{17}\text{H}_{34}\text{NO}_2$: 284.2590).

¹H NMR (600 MHz, CDCl_3) δ w ppm: 4.91 (d, $J = 7.1 \text{ Hz}$, 1H), 4.89 (d, $J = 7.0 \text{ Hz}$, 1H); 4.06 (br s, 2H); 3.86 (m, 4H); 3.70 (m, 2H); 3.53 (td, $J = 10.59 \text{ Hz}$, 4.20 Hz, 1H); 2.31 (m, 2H); 2.14 (m, 3H); 2.04 (pent. d, $J = 7.0 \text{ Hz}$, 2.60 Hz, 1H); 1.68 (m, 1H); 1.65 (m, 1H); 1.42 (m, 1H); 1.32 (m, 1H); 0.99 (m, 2H); 0.93 (t, $J = 6.6 \text{ Hz}$, 6H); 0.86 (td, $J = 12.4 \text{ Hz}$, 3.4 Hz, 1H); 0.80 (d, $J = 6.9 \text{ Hz}$, 3H).

¹³C NMR (CDCl_3) δ in ppm: 83.5; 81.0; 61.4; 60.7; 60.5; 56.1; 48.1; 40.4; 33.95; 31.2; 25.8; 22.7; 22.2; 22.1; 22.0; 21.0; 15.85.

General procedure of chloride anion exchange and synthesis of different salts with N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium cation

To the solution of N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium chloride in chloroform or dichloromethane or in water was added an appropriate salt (LiNTf_2 , KOTf, LiNPF_2 , NaBF_4 or NaPF_6) with 5–10% molar excess, as solution in deionized water. The reaction mixture was vigorously stirred for 24 h at 25°C . The mixture was then allowed to separation of phases. The organic layer was then washed many times with deionized water until no chloride was found potentiometrically. Organic solvent (if it was used) was then removed from the organic solution in vacuo and the residue was dried in vacuum dryer at 60°C for 24 h. The water level in the prepared salts after drying was less than 100 ppm.

N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium hexafluorophosphate, [M(2HEt)pyrr][PF₆]

Anion exchange was carried out between 3.2 g (0.010 mole) of [M(2HEt)pyrr][Cl] in 10 ml of CHCl_3 and 1.85 g (0.011 mole) of NaPF_6 in 5 ml of water, to give [M(2HEt)pyrr][PF₆] (4.07 g, 95%) as white solid.

¹H NMR (400 MHz, CDCl_3) δ in ppm: 4.68 (d, $J = 7.3 \text{ Hz}$, 1H); 4.59 (d, $J = 7.0 \text{ Hz}$, 1H); 4.03 (br s, 2H); 3.62 (m, 4H); 3.50 (m, 3H); 2.80 (br s, 1H); 2.25 (m, 2H); 2.15 (m, 2H); 2.08 (m, 1H); 2.04 (m, 1H); 1.66 (m, 2H); 1.42 (m, 1H); 1.32 (m, 1H); 0.99 (m, 2H); 0.92–0.94 (dd, $J = 7.0 \text{ Hz}$, 6H); 0.85 (m, 1H); 0.79 (d, $J = 6.7 \text{ Hz}$, 3H).

¹³C NMR (CDCl_3) δ in ppm: 84.3; 81.3; 60.9; 60.6; 60.4; 56.8; 48.0; 40.1; 34.0; 31.2; 25.8; 22.7; 22.2; 22.1; 22.0; 21.0; 15.6.

N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium tetrafluoroborate, [M(2HEt)pyrr][BF₄]

Anion exchange was carried out between 1.6 g (0.005 mole) of [M(2HEt)pyrr][Cl] in 5 ml of CH_2Cl_2 and 0.58 g (0.0053 mole) of NaBF_4 in 5 ml of water, to give [M(2HEt)pyrr][BF₄] (1.67 g, 91%) as white solid.

^1H NMR (400 MHz, CDCl_3) δ in ppm: 4.72 (d, $J = 7.0$ Hz, 1H); 4.64 (d, $J = 7.3$ Hz, 1H); 4.03 (br s, 2H); 3.66 (m, 4H); 3.54 (m, 2H); 3.50 (td, $J = 10.7$ Hz; 4.2 Hz, 1H); 2.27 (m, 2H); 2.14 (m, 2H); 2.10 (m, 1H); 2.04 (pent. d, $J = 7.01$ Hz, 2.52 Hz, 1H); 1.67 (m, 2H), 1.42 (m, 1H); 1.32 (m, 1H); 0.98 (m, 2H); 0.93 (dd, 6H); 0.85 (m, 1H); 0.80 (d, $J = 7.01$ Hz, 3H).

^{13}C NMR (CDCl_3) δ in ppm: 84.1; 81.1; 61.0; 60.5; 60.3; 56.7; 48.1; 40.2; 34.0; 31.2; 25.8; 22.7; 22.3; 22.2; 22.0; 21.0; 15.7.

N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium trifluoromethanesulfonate, [M(2HEt)pyrr][OTf]

Anion exchange was carried out between 2.56 g (0.0080 mole) of [M(2HEt)pyrr][Cl] in 8 ml of CHCl_3 and 1.33 g (0.0085 mole) of LiOTf in 5 ml of water, to give [M(2HEt)pyrr][OTf] (3.26 g, 94%) as white solid.

^1H NMR (400 MHz, CDCl_3) δ in ppm: 4.74 (d, $J = 7.08$ Hz, 1H); 4.66 (d, $J = 7.33$ Hz, 1H); 4.33 (t, $J = 5.37$ Hz, 1H); 4.02 (d, $J = 4.6$ Hz, 2H); 3.68 (m, 4H); 3.56 (m, 2H); 3.49 (td, $J = 10.5$ Hz; 4.1 Hz, 1H); 2.26 (m, 2H); 2.16 (m, 2H); 2.10 (m, 1H); 2.05 (m, 1H); 1.67 (m, 1H), 1.41 (m, 1H); 1.31 (m, 1H); 1.0 (m, 2H); 0.93 (dd, $J = 6.8$ Hz, 6H); 0.87 (m, 1H); 0.79 (d, $J = 7.08$ Hz 3H).

^{13}C NMR (CDCl_3) δ in ppm: 122.1; 118.9; 84.1; 81.2; 61.0; 60.5; 60.4; 56.5; 48.1; 40.2; 34.0; 31.2; 25.8; 22.7; 22.2; 22.1; 22.0; 21.0; 15.7.

N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium bis(trifluoromethylsulfonyl)imide, [M(2HEt)pyrr][NTf₂]

Anion exchange was carried out between 6.39 g (0.02 mole) of [M(2HEt)pyrr][Cl] and 6.31 g (0.022 mole) of LiNTf₂ in 10 ml of deionized water to give 10.15 g (90%) of [M(2HEt)pyrr][NTf₂] as colourless liquid ($d^{25} = 1.3156$ g/cm³, $n^{20} = 1.4503$).

^1H NMR (600 MHz, CDCl_3) δ in ppm: 4.69 (d, $J = 7.12$ Hz, 1H); 4.59 (d, $J = 7.12$ Hz, 1H); 4.01 (br s, 2H); 3.62 (m, 4H); 3.50 (m, 3H); 2.24 (m, 2H); 2.15 (m, 2H); 2.05 (m, 2H); 1.67 (m, 2H), 1.40 (m, 1H); 1.32 (m, 1H); 0.99 (m, 2H); 0.93 (dd, $J = 6.8$ Hz, 6H); 0.87 (m, 1H); 0.79 (d, $J = 6.96$ Hz 3H).

^{13}C NMR (CDCl_3) δ in ppm: 122.9; 120.8; 118.7; 116.5; 84.2; 81.2; 60.8; 60.6; 60.5; 56.6; 48.0; 40.1; 33.9; 31.1; 25.8; 22.6; 22.2; 22.0; 21.8; 20.9; 15.5.

N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium bis(pentafluoroethylsulfonyl)imide, [M(2HEt)pyrr][NPF₂]

Anion exchange was carried out between 4.2 g (0.013 mole) of [M(2HEt)pyrr][Cl] and 5.4 g (0.014 mole) of LiNPF₂ in 10 ml of deionized water to give 7.77 g (90%) of [M(2HEt)pyrr][NPF₂] as colourless liquid ($d^{25} = 1.3170$ g/cm³, $n^{20} = 1.4507$).

^1H NMR (600 MHz, CDCl_3) δ in ppm: 4.67 (d, $J = 6.98$ Hz, 1H); 4.58 (d, $J = 6.98$ Hz, 1H); 4.0 (br s, 2H); 3.62 (m, 4H); 3.49 (m, 3H); 3.18 (t, $J = 5.03$ Hz, 1H); 2.23 (m, 2H); 2.15 (m, 2H); 2.04 (m, 1H); 1.67 (m, 2H), 1.40 (m, 1H); 1.32 (m, 1H); 0.98 (m, 2H); 0.92 (d, $J = 6.82$ Hz, 6H); 0.86 (m, 1H); 0.78 (d, $J = 6.98$ Hz, 3H).

^{13}C NMR (CDCl_3) δ in ppm: 118.9; 117.0; 111.8; 111.6; 84.2; 81.2; 60.8; 60.6; 60.4; 56.6; 48.0; 40.1; 33.9; 31.1; 25.8; 22.6; 22.2; 22.0; 21.8; 20.9; 15.5.

RESULTS AND DISCUSSION

Synthesis of chiral N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium salts from (-)-menthol, consisted of three stages, presented in Figure 1. In the first, (1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-chloromethylether was formed by bubbling a gaseous hydrochloride through the mixture of (-)-menthol, paraformaldehyde in toluene. In the next stage the prepared and purified chiral ether was used to the quaternization of N-(2-hydroxyethyl)pyrrolidine with the formation of N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium chloride, [M(2HEt)pyrr][Cl] with 90% yield. We had an evidence of successfully quaternization from HRMS analysis in high resolution positive ionization mode. Mass found for cation was in high compliance with mass calculated for N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium cation.

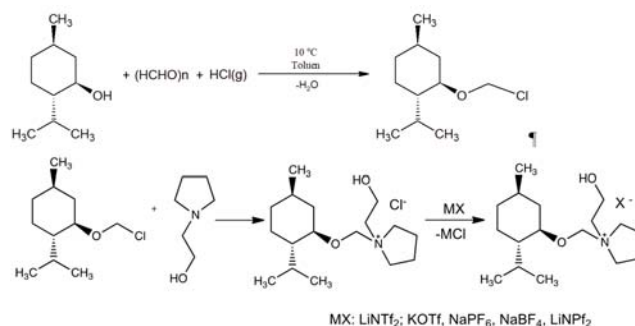


Figure 1. Synthesis path of chiral pyrrolidinium salts based on (-)-menthol; Tf = CF_3SO_2 ; Pf = $\text{C}_2\text{F}_5\text{SO}_2$

The last stage of the synthesis process concerned the exchange of chloride anion to another one. The yield of the reaction of anion exchange was in the range of 89–95% for individual anion.

The prepared salts were identified by NMR analysis. Comparison of ^1H NMR spectra for salts with different anions was presented in Figure 2. We can see notable differences in the chemical shifts of the protons of methylene groups linked to the nitrogen atom for salt with Cl^- anion and with other anions. For example, value of shift for protons H11 adjacent to the oxygen atom (Fig. 2) are 4.91 and 4.89 ppm (specific two doublets) with Cl^- anion, whereas values are 0.2–0.3 ppm lower for BF_4^- , OTf^- , PF_6^- , NTf_2^- and NPF_2^- anions. Additionally, the distance between these two doublets in spectra is longer for the bulkier anions, that indicate the less similarity (greater non-identity) of that both protons. Coupling constants values are similar for each anion and is between 6.98 and 7.33 Hz.

Values of chemical shift for protons (H14 and H17 in Fig. 2) of methylene groups in pyrrolidine ring, adjacent to the nitrogen atom are 3.85 ppm with Cl^- anion and 3.61–3.68 ppm with other anions. Similar differences concern protons of methylene group H12 for which the chemical shift is 3.70 ppm with Cl anion and between

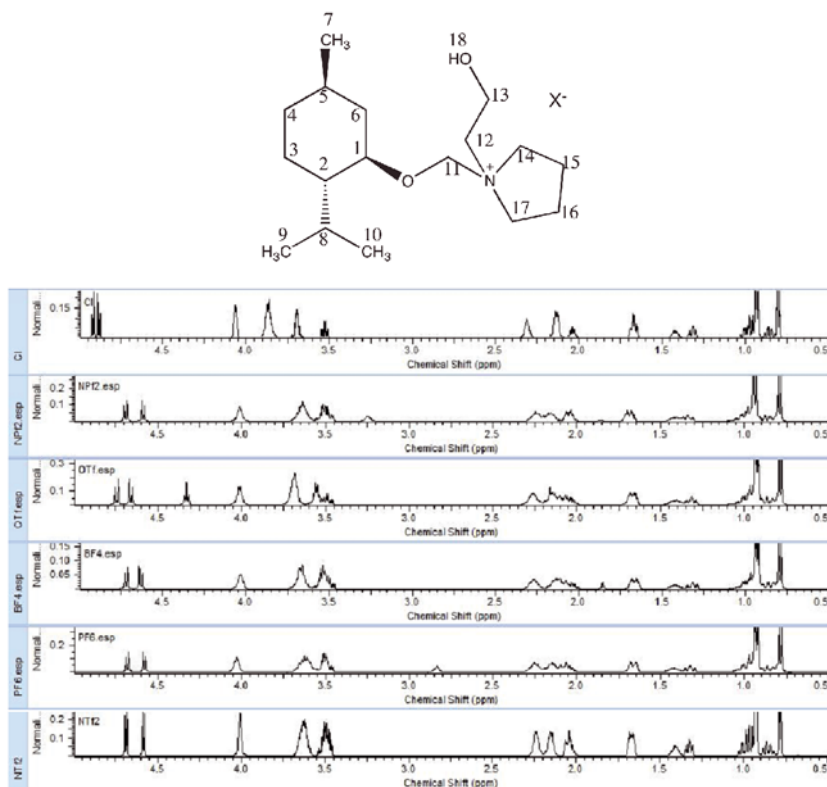


Figure 2. Comparison of ^1H NMR spectra for N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium cation depending on the combined anion (from the top: X = Cl, NPF_2 , OTf, BF_4 , PF_6 , NTf_2)

3.49 and 3.56 ppm for other anions. These differences in chemical shifts by changing of Cl anion to the bulky anions can be ascribed to the electrostatic and steric interactions, which primarily effect on electron density near the quaternary nitrogen atom. Differences in chemical shifts of protons of the other groups with change of anion of the salt are rather negligible.

Two of the pyrrolidinium salts, with NTf_2 and NPF_2 anions, were liquids at room temperature and they formed glasses below -50°C . This implies that these two salts are ionic liquids, according to ILs definition. They can be used as chiral solvents in organic synthesis, even at temperatures below 0°C . However, pyrrolidinium salts, with PF_6 , BF_4 , OTf and Cl anion, melted at temperatures close to 100°C (Table 1). $[\text{M}(2\text{HEt})\text{pyrr}][\text{Cl}]$ was characterized with the highest melting point, 112°C . Based on DSC analysis, which was performed in the repeated cooling/heating sequence we have also detected crystallization in the second cooling option for $[\text{M}(2\text{HEt})\text{pyrr}][\text{BF}_4]$ and $[\text{M}(2\text{HEt})\text{pyrr}][\text{PF}_6]$ salts. Crystallization temperatures were lower than melting points and were 63.9°C and 59.5°C respectively.

All pyrrolidinium salts were chiral compounds, with negative values of specific rotation, such as (-)-menthol used to their synthesis (Table 1). The variety of specific rotation value is a consequence of different molar mass of anion in individual salts.

Attention should be paid to thermal stability which was measured by thermogravimetric analysis (Fig. 3). Temperatures of 5% weight loss were determined (Table 1). The results implied that pyrrolidinium salts start to decompose at temperatures near 200°C , except of $[\text{M}(2\text{HEt})\text{pyrr}][\text{Cl}]$ which decomposed at temperature below 150°C . The salts can be arranged according to rising trend of their thermal stability as follows: $\text{Cl} < \text{BF}_4 \sim \text{OTf} \sim \text{PF}_6 < \text{NTf}_2 < \text{NPF}_2$. Moreover, it is notable two-stage decomposition of pyrrolidinium salts with OTf, NTf_2 and NPF_2 anions. The percentage mass loss at first decomposition step was established approximately 36.2%; 27.7% and 23.5%, for salts with OTf, NTf_2 and NPF_2 anion respectively. Considering molar weight of these salts, an elimination of fragment with molar mass close to 156 was noted, which can suggest elimination of menthol fragment.

Table 1. A summary of physicochemical properties of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium salts

Salt abbreviation	M_p [$^\circ\text{C}$]	T_g [$^\circ\text{C}$]	$[\alpha]_D^{20}$	$T_d^{5\%}$ [$^\circ\text{C}$]
$[\text{M}(2\text{HEt})\text{pyrr}][\text{Cl}]$	112.0	nd	-63.9	153.3
$[\text{M}(2\text{HEt})\text{pyrr}][\text{PF}_6]$	99.8	nd	-48.6	198.9
$[\text{M}(2\text{HEt})\text{pyrr}][\text{BF}_4]$	101.7	nd	-56.9	209.9
$[\text{M}(2\text{HEt})\text{pyrr}][\text{OTf}]$	104.8	nd	-47.4	190.0
$[\text{M}(2\text{HEt})\text{pyrr}][\text{NTf}_2]$	nd	-50.2	-51.8	214.4
$[\text{M}(2\text{HEt})\text{pyrr}][\text{NPF}_2]$	nd	-52.2	-31.4	220.4

nd = not detectable; $T_d^{5\%}$ – temperature of 5% mass loss.

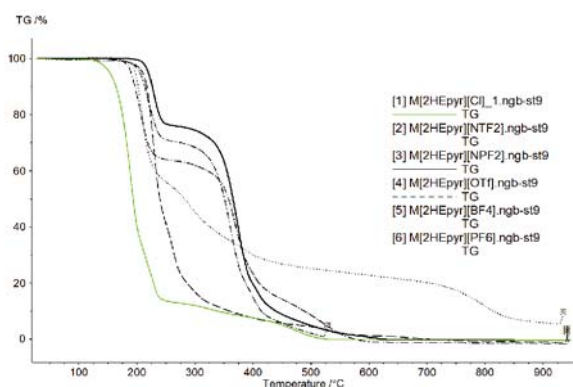


Figure 3. Thermogravimetric curves of N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium salts

Additionally, the EI mass spectrum for pure salt [M(2HEt)pyrr][NTf₂] was recorded in positive ion mode. EI method uses very high temperatures to evaporate the sample, which is accompanied by substantial decomposition. Figure 4 shows this spectrum as a representative example. The spectrum not only determines the fragmentation pathway of cation, but also characterizes the stability of ions in the gas phase based on their relative abundance. In the spectrum of [M(2HEt)pyrr][NTf₂] we can observe low intensity ion $m/z = 284$ corresponding to the [M(2HEt)pyrr] cation. Moreover, mass spectrum

showed the presence of average intensity ion $m/z = 128$, which corresponds to elimination of menthol fragment (mass 156) from the cation. The ion $m/z = 156$ is not observed in the spectrum, what suggests that this ion is unstable in gas phase. This observation may be a confirmation of elimination of the menthol fragment at the first decomposition stage.

Chiral pyrrolidinium salts [M(2HEt)pyrr][NTf₂] and [M(2HEt)pyrr][NPF₂] were in the liquid state at room temperature and typical properties were also determined for them as for other liquids in relation to temperature (Table 2, Fig. 5). Both ionic liquids have higher density than water, but values for both are similar. For example, density at temperature of 23°C is 1.1356 g · cm⁻³ and 1.1370 g · cm⁻³ for [M(2HEt)pyrr][NTf₂] and [M(2HEt)pyrr][NPF₂] respectively. More noticeable differences were found in dynamic viscosity. Ionic liquid with NTf₂ anion has twofold lower viscosity than that with NPF₂ anion at temperature of 23°C. However, the viscosities of these ionic liquids decrease significantly with increase of temperature as was shown in Figure 5 and obtain similar values for both at higher temperatures. These two chiral pyrrolidinium ionic liquids have the potential utility as chiral solvents and catalysts in the organic synthesis. We chose to test Diels-Alder reaction, because it is one of the broad useful reactions. Moreover, it was known that specific interactions between the reactants of Diels-Alder

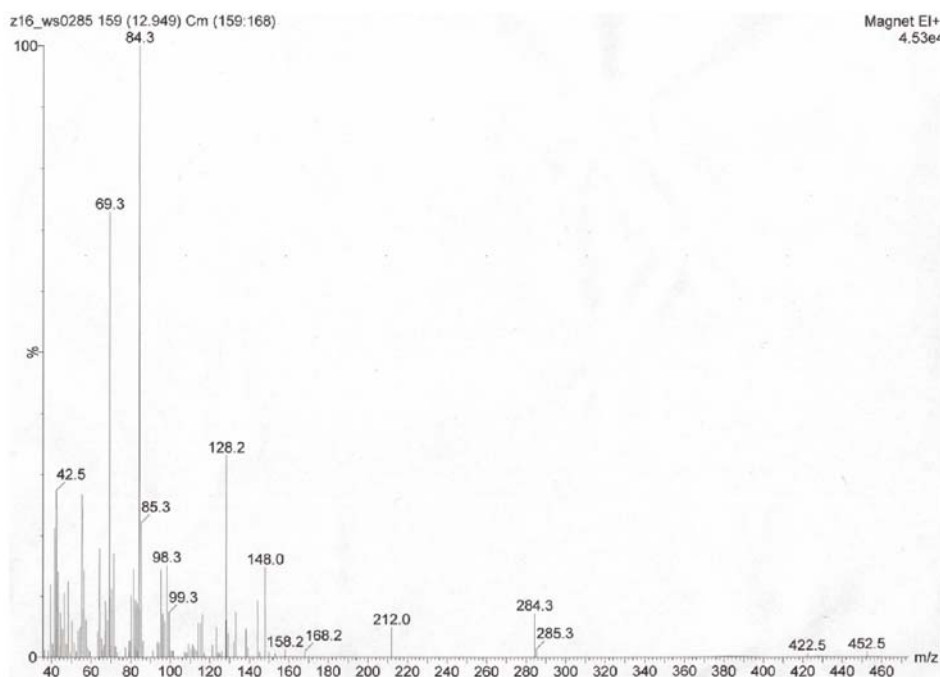


Figure 4. EI mass spectrum of [M(2HEt)pyrr][NTf₂] in positive ionization mode

Table 2. The dependence of dynamic viscosity and density of [M(2HEt)pyrr][NTf₂] and [M(2HEt)pyrr][NPF₂] on temperature

Temperature [°C]	Dynamic viscosity [Pa·s]		Density [g·cm ⁻³]	
	[M(2HEt)pyrr][NTf ₂]	[M(2HEt)pyrr][NPF ₂]	[M(2HEt)pyrr][NTf ₂]	[M(2HEt)pyrr][NPF ₂]
20	1.8229	3.8682	1.3168	1.3182
23	1.3953	2.9066	1.3156	1.3170
25	1.1651	2.4122	1.3148	1.3162
30	0.7814	1.5397	1.3128	1.3142
40	0.3871	0.6942	1.3088	1.3102
50	0.2175	0.3556	1.3048	1.3062
60	0.1437	0.2134	1.3008	1.3022
70	0.1157	0.1641	1.2968	1.2982
80	0.1103	0.1438	1.2928	1.2942

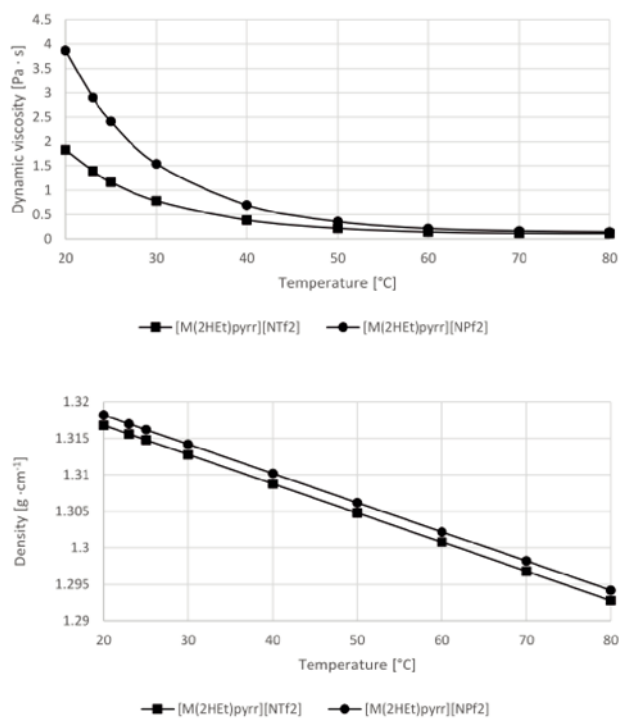


Figure 5. Dependence of dynamic viscosity and density on temperature for [M(2HEt)pyrr][NTf₂] and [M(2HEt)pyrr][NPF₂] salts

reaction and the cation of ionic liquid^{29–31} are responsible for accelerate it and enhance its selectivity in ionic liquids in comparison to molecular solvents and chiral cation could make these interactions more specific. We tested the chiral ionic liquid [M(2HEt)pyrr][NTf₂] as medium of Diels-Alder reaction between cyclopentadiene and few dienophiles – methyl acrylate (1a), dimethyl maleate (1b) and ethyl-vinyl ketone (1c) (Fig. 6). The reaction was conducted at room temperature on 1 mmol scale and was monitored by gas chromatography to determine yield and stereoselectivity. Additionally, for the reaction of 1a or 1c as dienophile, the enantioselectivity was checked by using chiral GC columns. The results were presented in Figure 7.

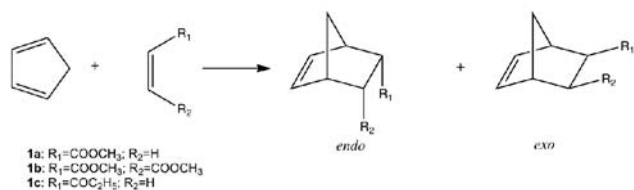


Figure 6. The reaction of cyclopentadiene and three dienophiles

The reaction proceeded with good yield of cycloaddition product. Stereoselectivity *endo/exo* was 4.9, 3.9 and 5.0 for 1a, 1b and 1c respectively. In comparison to achiral pyrrolidinium³² and sulfonium³³ or phosphonium³⁴ cations we achieved higher yield and stereoselectivity. However, chiral cation didn't allow us to obtain noticeable enantiomeric excess.

Therefore, currently our studies concern the use of these chiral pyrrolidinium ionic liquids as solvents of chiral catalysts, to improve their stabilization, application possibilities in asymmetric synthesis and for recyclability.

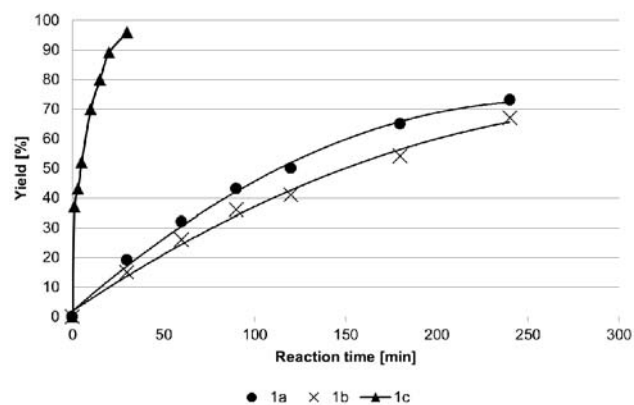


Figure 7. The dependence of product yield on the reaction time for the reaction of cyclopentadiene and dienophile: 1a, 1b and 1c

CONCLUSION

The series of chiral pyrrolidinium salts composed of N-(2-hydroxyethyl)-N-[(1*R*,2*S*,5*R*)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium cation and six different anions (Cl, BF₄, PF₆, OTf, NTf₂, NPF₂) were synthesized with good yield. Chiral substituent in the cation was derived from (-)-menthol as inexpensive chiral precursor. NMR analysis indicated a significant effect of the change of chloride anion to the bulkier anions on chemical shift of protons adjacent to the quaternary nitrogen atom of the pyrrolidine ring. Physicochemical properties also changed with the type of anion. Salts with NTf₂ and NPF₂ anion were liquids at room temperature and characterized by the highest thermal stability among obtained salts. It was shown that they can be used as reaction media in Diels-Alder reaction and proved the high yield and diastereoselectivity.

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