Quinine Based Ionic Liquids: A Tonic for Base Instability

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Abstract

Six basic ionic liquids were synthesised from the natural molecule quinine, including one room temperature ionic liquid. The thermal properties were studied and the basicity analysed by Hammett measurements. The properties are discussed in relation to the crystal structure of one of the salts, [C_4Qn][NTf_2] (**2c**) and electron density models generated using Spartan. The ionic liquids were shown to catalyse the Knoevenagel condensation of Malononitrile and Benzaldehyde.

Keywords: Basic ionic liquids, Base stable ionic liquids, Fluorescent ionic liquids, Chiral ionic liquids, Quinine, Base catalysis, Knoevenagel condensation.

1. Introduction

Ionic liquids are materials composed entirely of ions which form stable liquids at any temperature, 100 °C is frequently defined as the upper melting point limit [1]. Ionic liquids are well known to have favourable physical properties including high thermal stability, low flammability and negligible vapour pressure, and this has led to them being hailed as green solvents as they pose lower immediate hazard than conventional organic solvents [2]. Despite the apparent stability, the imidazolium cation, the most common cation reported for preparing ionic liquids, is extremely sensitive to base [3]. The heterocyclic ring is easily deprotonated at C2 to form an N-heterocyclic carbene. This limits the use of ionic liquids, as it prevents their successful recycle in base catalysed reactions. Basic ionic liquids can be prepared by locating the basicity on the anion. This can create strong basicity, but often leads to instability as the anion can attack the cation, causing the breakdown of the ionic liquid [4]. Basic ionic liquids of greater stability can be prepared by locating basicity on the cation [5], usually on free Lewis basic sites. Examples of this class includes ionic liquids synthesised from diaminoalkanes [6] and 4-dimethylaminopyridine (DMAP) [7,8]. Diaminoalkane ionic liquids suffer from a lack of selective alkylation which complicates their synthesis. A mixture of mono and dialkylated species can be formed which are difficult to separate [6]. DMAP ionic liquids have reduced basicity due to withdrawal of electron density from the Lewis base by the cation [7,8]. We have previously had some success stabilising basic ionic liquids by using binary ionic liquids containing small amounts of alkoxide anions [9], and by heterogenising phosphonium hydroxide ionic liquids within silica and titania gels *via* the sol-gel process [10,11]. This manuscript focusses on a third approach, the use of quinine derived cations.

Quinine is a natural molecule which can be extracted from the bark of cinchona trees [12]. Quinine salts are well known as phase transfer catalysts, most famously in the Sharpless asymmetric dihydroxylation [13]. Quinine halides are often used in the presence of strong bases such as KOH [14] and sodium *tert*-butoxide [15]. This indicates that the cation is relatively stable under basic conditions. This stability, combined with the developments in synthesising ionic liquids from renewables [16,17,18,19] makes quinine an ideal starting material for base stable ionic liquids. Quinine has been tethered to an imidazolium cation [20], and recently high melting quinine ionic liquids were synthesised and tested for enantiomeric recognition [21]. To the best of our knowledge quinine ionic liquids melting below 100 °C are unknown.

This work comprises the synthesis of six quinine ionic liquids, including one which is low melting and one room temperature ionic liquid. Quinine reacts preferentially at the non-aromatic nitrogen, rather than the quinoline nitrogen, eliminating problems of low selectivity seen in the synthesis of previous basic ionic liquids [6] and the low base stability of aromatic cations used in conventional ionic liquids [22,23]. The use of the bistriflimide anion, and ether groups in the alkyl chain of the cation, lowers the melting points by a reduction in hydrogen bonding and an increase in flexibility, disrupting ion packing. The quinine ionic liquids have a free nitrogen atom which can act as a base, allowing them to be applied as basic catalysts, this has been demonstrated for the Knoevenagel condensation between malononitrile and benzaldehyde.

2. Materials and methods

2.1 Materials

Solvents were purchased from Sigma-Aldrich and used as supplied without further purification. Quinine (98 %) was purchased from Tokyo Chemical Industry UK, iodomethane (99 %), iodobutane (99 %), bromobutane (99 %), iodohexane (98 %), bromohexane (98 %), bromooctane (99 %), 2-bromoethyl methyl ether and 1-bromo-2-(2-methoxyethoxy)ethane (95 %) were purchased from Sigma-Aldrich. Bis(trifluoromethane)sulfonimide lithium salt was purchased from 3M. Malononitrile (99 %) and benzaldehyde (99 %) were purchased from Alfa Aesar.

2.2 NMR spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra (assigned by Distortionless Enhancement by Polarization Transfer, DEPT), fluorine nuclear magnetic resonance (^{19}F NMR) spectra and phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded at 300 MHz using a Bruker Ultrashield 300 MHz spectrometer. Two-dimensional nuclear magnetic resonance (2-D NMR), ^{1}H-^{1}H correlation spectroscopy (COSY) and ^{1}H-^{13}C heteronuclear single quantum coherence (HSQC) were recorded at 400 MHz using a Bruker Ultrashield 400 MHz spectrometer. Spectra were assigned using 2D NMR and comparison with the literature.

2.3 FTIR spectroscopy

FTIR spectra were recorded on Thermo Nicolet Nexus 670 and Perkin Elmer Spectrum Two.

2.4 Thermogravimetric analysis (TGA)

TGA measurements were carried out using a TGA Q5000 IR thermogravimetric analysis from TA Instruments. The samples were heated in N2 gas with a balance purge flow of 25 mL/min and a sample purge flow of 10 mL/min, with a heating rate of 10 °C per minute within a temperature range of 30 °C to 400 °C.

2.5 Differential scanning calorimetry (DSC)

DSC measurements were made on a DSC Q2000 from TA Instruments. The samples were heated in an aluminium pan with gas 1 helium, gas 2 N_2, both with flow 50 mL/min, temperature cycled between – 90 °C and 200 °C at 20 °C per minute.

2.6 Spartan calculations

Spartan calculations were performed using SPARTAN '14 Quantum Mechanics Driver: (Win/64b) Release 1.1.4. Method: RB3LYP. Basis set: 6-31G(D).

2.7 Synthesis and characterisation of quinine ionic liquids

The chemical structure and abbreviation of all quinine ionic liquids are given in Figure 1. The structure of all compounds was confirmed by ^{1}H, ^{13}C, ^{19}F and where appropriate, by the 2D 1H-13C HSQC and 2D 1H-1H Cosy NMR sequences as well as by mass spectrometry and elemental analysis. Spectra are available in ESI section 3 and 4. Synthesis of halides were adapted from Berkessel *et. al.* [24].

2.7.1. Synthesis of 1-N-methyl quininium iodide: [MeQn][I] (1a)

Quinine (2.09 g, 6.44 mmol) was dissolved in methanol (MeOH, 60 mL) to form a colourless solution. To this was added methyl iodide (1.26 g, 8.90 mmol) and the solution was stirred overnight at room temperature. The solvent was removed *via* rotary evaporation and dried for 30 minutes to yield a golden yellow solid. The solid was recrystallized from boiling MeOH (~ 7 mL). The recrystallized solid was washed with diethyl ether and dried overnight under high vacuum to yield an off-white solid. [MeQn][I] (**1a**) yield = 2.98 g, 6.40 mmol, 99.4 %.

Quinine (0.25 g, 0.774 mmol) was dissolved in Me-THF (10 mL). To this was added methyl iodide (0.082 g, 0.58 mmol). The flask was capped and stirred at room temperature overnight. During this time a white precipitate formed which was filtered by gravity and washed with Me-THF. The precipitate was recrystallized from boiling methanol (~0.6 mL), filtered and washed with a small amount of diethyl ether. The solid was dried overnight under high vacuum. [MeQn][I] (**1a**) yield = 0.10 g, 0.217 mmol, 37.6 %.

ESI-MS *m/z:* Found 339. 1968 (M^+), calcd. for $C_{21}H_{27}N_2O_2$: 339.2062. Found 805.3190 ($M^+ + M^+ + M^-$), calcd. for $(C_{21}H_{27}N_2O_2)_2I$: 805.3180.

^{1}H-NMR (300 MHz, DMSO-d_6): δ: 1.30-1.37 (m, H, $H5_{endo}$), 1.89-1.97 (m, H, $H7_{endo}$), 2.04-2.05 (m, H, $H5_{exo}$), 2.10-2.16 (m, 2H, $H6_{endo}$, H4), 2.79-2.87 (m, H, H3), 3.38 (s, 3H, HA), 3.46-3.52 (m, H, $H7_{exo}$), 3.61-3.80 (m, 3H, H2, $H6_{exo}$), 4.02 (s, 3H, $OC\underline{H_3}$), 4.08-4.16 (m, H, H8), 5.00-5.16 (m, 2H, H11, H11′), 5.69-5.81 (m, H, H10), 6.25 (d, 3.20 Hz, H, H9), 6.53 (d, 3.39 Hz, H, $O\underline{H}$), 7.21-7.22 (m, H, H19), 7.47 (dd, 2.45 Hz, 9.23 Hz, H, H17), 7.71 (d, 4.52 Hz, H, H14), 8.00 (d, 9.23 Hz, H, H20), 8.79 (d, 4.52 Hz, H, H13). ^{13}C-NMR (300 MHz, DMSO-d_6): δ: 19.74 (C7), 24.99, (C5), 26.28 (C4), 37.92 (C3), 49.24 (CA), 54.59 (C6) 56.02 ($O\underline{C}H_3$), 64.21 (C2), 64.26 (C8), 67.24 (C9), 101.93 (C17), 116.93 (C11), 120.35 (C19), 122.01 (C14), 125.55 (C16), 131.84 (C20), 138.41 (C10), 144.02 (C21), 144.24 (C15), 147.86 (C13), 157.78 (C18).

2.7.2. Synthesis of 1-N-methyl quininium bistriflimide: [MeQn][NTf_2] (1c)

To 1-*N*-methyl quininium iodide, [1-*N*-MeQn][I] (**1a**) (2.42 g, 6.40 mmol) dissolved in dichloromethane (DCM, 5 mL) was added lithium bistriflimide (Li(NTf_2), 2.42g, 8.32 mmol) dissolved in deionised water (5 mL). More water (5 mL) was added and to aid solubility as was MeOH (5 mL). The two-phase mixture was heated to 60 °C with stirring and with a reflux condenser fitted. The solid dissolved and orange droplets were visible. After 19 hours the reaction was stopped and the layers allowed to settle. The aqueous layer was decanted off. Fresh deionised water (10 mL) was added and the solution heated at 60 °C with stirring for 30 minutes. The water was decanted off after this time. This was repeated twice more. Then DCM was added followed by deionised water (10 mL) and the mixture stirred for 30 minutes before decanting off the aqueous phase. The organic phases were combined and washed twice more in a separating funnel. The combined aqueous layers were extracted twice with DCM. All organic phases were combined and dried by rotary evaporation to yield a yellow solid. This was further dried under high vacuum overnight. [MeQn][NTf_2] (**1c**) yield = 3.57 g, 5.77 mmol, 90.2 %.

Found C 44.57, H 4.17, N 6.78, S10.08. Calcd for $C_{23}H_{27}F_6N_2O_6S_2$: C 44.58, H 4.39, N 6.78, S 10.35 %. ESI-MS *m/z:* Found 339.1877 (M^+), calcd. for $C_{21}H_{27}N_2O_2$: 339.2062. Found 279.9173 (M^-), calcd. for $C_2F_6NO_4S_2$: 279.9173. TGA = 263 °C. m.p. = 130 °C. T_g = 55 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ: 1.31-1.39 (m, H, $H5_{endo}$), 1.89-1.97 (m, H, $H7_{endo}$), 2.04-2.05 (m, H, $H5_{exo}$), 2.12-2.18 (m, 2H, $H6_{endo}$, H4), 2.77-2.85 (m, H, H3), 3.36-3.47 (m, H, $H7_{exo}$), 3.40 (s, 3H, HA), 3.63-3.70 (m, 3H, H2, $H6_{exo}$), 4.01 (s, 3H, $OC\underline{H_3}$), 4.06-4.14 (m, H, H8), 5.00-5.16 (m, 2H, H11, H11'), 5.70-5.81 (m, H, H10), 6.24 (d, 2.64 Hz, H, $O\underline{H}$), 6.57 (d, 3.20 Hz, H, H9), 7.21-7.22 (m, H, H19), 7.47 (dd, 2.45 Hz, 9.23 Hz, H, H17), 7.72 (d, 4.52 Hz, H, H14), 8.01 (d, 9.23 Hz, H, H20), 8.30 (d, 4.52 Hz, H, H13). ^{13}C-NMR (300 MHz, DMSO-d_6): δ: 19.71 (C7), 25.00 (C5), 26.30 (C4), 37.98 (C3), 49.14 (CA), 54.62 (C6), 55.87 ($O\underline{C}H_3$), 64.31 (C2, C8), 67.19 (C9), 101.93 (C17), 116.89 (C11), 119.88 (q, 326.44 Hz, $\underline{C}F_3$) 120.34 (C19), 122.01 (C14), 125.55 (C16), 131.86 (C20), 138.38 (C10), 144.03 (C21), 144.24 (C15), 147.84 (C13), 157.79 (C18). ^{19}F-NMR (300 MHz, DMSO-d_6): δ: - 79.18. IR (KBr Disc): $\bar{\nu}$ (cm^{-1}) = 3094 (OH), 3001 (CH), 2958 (CH), 2838 (CH), 1625 (alkene C=C), 1592 (C=N), 1558, 1511 (aromatic C=C), 1476, 1433, 1419, 1243, 1195 (C-O), 1135, 1057, 831, 603, 571, 505.

2.7.3. Synthesis of 1-N-butyl quininium iodide: [C_4Qn][I] (2a)

Quinine (1.99 g, 6.15 mmol), was dissolved in MeOH (55 mL) to form a colourless solution. To this was added butyl iodide (1.49 g, 8.12 mmol). The solution was stirred at room temperature for 60 hours. TLC, eluting with 5:1 chloroform: methanol showed no reaction (Quinine only, Rf 0.45). The reaction was then heated to 40 °C with a reflux condenser for 24 hours and then 60 °C for 48 hours until TLC showed no further reaction progress. Product spot had Rf 0.07. Solvent was removed on rotary evaporator to yield a yellow solid. The solid was recrystallized twice with boiling MeOH to leave the pure product. The yellow solid was dried under high vacuum overnight. [C_4Qn][I] (**2a**) yield = 0.52 g, 1.03 mmol, 16.7 %.

Quinine (1.01 g, 3.10 mmol) was suspended in Me-THF (15 mL). To this was added butyl iodide (0.55 g, 2.98 mmol). A condenser was fitted and the mixture was stirred under reflux for 20 hours. During this time a pink precipitate formed in the purple solution. The precipitate was filtered by gravity and washed with Me-THF so that it became white. The solid was dried by rotary evaporation. [C_4Qn][I] (**2a**) yield = 0.79 g, 1.56 mmol, 50.4 %.

ESI-MS *m/z:* Found 381.2276 (M^+), calcd. for $C_{24}H_{33}N_2O_2$: 381.2531. Found 889.4129 ($M^+ + M^+ + M^-$), calcd. for $(C_{24}H_{33}N_2O_2)_2I$: 889.4118.

^{1}H-NMR (300 MHz, $CDCl_3$): δ: 0.95 (t, 7.35 Hz, 3H, HD), 1.24-1.33 (m, H, $H5_{endo}$), 1.52 (sext, 7.35 Hz, 2H, HC), 1.79-1.86 (m, 2H, HB), 1.89-1.94 (m, 2H, $H7_{endo}$, $H5_{exo}$), 2.03-2.09 (m, 2H, $H6_{endo}$, H4), 2.65 (br s, H, H3), 2.80 (br s, H, $H7_{exo}$), 3.08-3.13 (m, H, $H6_{exo}$), 3.38-3.44 (m, H, H2), 3.51-3.59 (m, H, H2′), 3.76-3.97 (m, 2H, HA), 3.89 (s, 3H, $OC\underline{H_3}$), 4.31 (t, 10.47 Hz, H, H8), 4.91-5.02 (m, 2H, H11, H11'), 5.42-5.43 (m, 2H, H9, H10), 6.37 (s, H, $O\underline{H}$), 7.00 (d, 2.26 Hz, H, H19), 7.30 (dd, 2.45 Hz, 6.97 Hz, H, H17) 7.61 (d, 4.52 Hz, H, H14), 7.94 (d, 9.23 Hz, H, H20), 8.61 (d, 4.52 Hz, H, H13). ^{13}C-NMR (300 MHz, $CDCl_3$): δ: 12.86 (CD), 19.17 (C7), 20.36 (CC), 24.04 (CB, C5), 25.16 (C4), 36.45 (C3), 53.12 (C6), 55.23 ($O\underline{C}H_3$), 59.90 (C2), 60.57 (C8), 62.69 (CA) 65.60 (C9), 100.34 (C17), 116.70 (C11), 119.70 (C19), 120.14 (C14), 124.64 (C16), 131.01 (C20), 135.66 (C10), 142.25 (C21), 143.01 (C15), 146.52 (C13), 157.20 (C18).

2.7.4. Synthesis of 1-N-butyl quininium bistriflimide: [C_4Qn][NTf_2] (2c)

1-*N*-butyl quininium iodide, [1-*N*-C_4Qn][I] (**2a**) (0.48 g, 0.945 mmol) was dissolved in MeOH (1 mL). To this was added Li(NTf_2) (0.32 g, 1.14 mmol), dissolved in deionised water (0.5 mL). The two-phase mixture was stirred vigorously and heated to 70 °C for 18 hours. Water was decanted off and DCM added. Fresh water was added and the mixture heated with stirring for 20 minutes. The water was then decanted off. This was repeated twice more. The organic layer was washed twice more with water in a separating funnel. The combined aqueous layers were extracted twice with DCM. The organic layers were combined and solvent removed by rotary evaporation to yield a yellow glass. This was dried overnight under high vacuum. [C_4Qn][NTf_2] (**2c**) yield = 0.58 g, 0.861 mmol, 93.8 %.

Found C 47.12, H 5.65, N 6.41, S 9.35. Calcd for $C_{26}H_{33}F_6N_3O_6S_2$: C 47.19, H 5.03, N 6.35, S 9.69. ESI-MS *m/z:* Found 381.2511 (M^+), calcd. for $C_{24}H_{33}N_2O_2$: 381.2531. Found 279.9173 (M^-), calcd. for $C_2F_6NO_4S_2$: 279.9173. TGA = 224 °C. m.p. > 190 °C. T_g = 18 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ: 0.92 (t, 7.16 Hz, 3H, HD), 1.20-1.30 (m, H, $H5_{endo}$), 1.42 (sext, 6.97 Hz, 2H, HC), 1.79-1.83 (m, 2H, HB), 1.90-2.00 (m, 2H, $H7_{endo}$, $H5_{exo}$), 2.07-2.17 (m, 2H, $H6_{endo}$, H4), 2.74 (br s, H, H3), 3.02-3.07 (m, H, $H7_{exo}$), 3.35-3.66 (m, 5H, H2, $H6_{exo}$, HA), 3.82 (s, 3H, $OC\underline{H_3}$), 4.26 (t, 11.30 Hz, H, H8), 4.92-5.01 (m, 2H, H11, H11'), 5.36-5.51 (m, 2H, H9, H10), 6.13 (s, H, $O\underline{H}$), 6.91 (s, H, H19), 7.30 (d, 8.85 Hz, H, H17), 7.61 (d, 4.14 Hz, H, H14), 7.90 (d, 9.23 Hz, H, H20), 8.53 (d, 4.14 Hz, H, H13). ^{13}C-NMR (300 MHz, $CDCl_3$): δ: 12.31 (CD), 18.83 (C7), 19.93 (CC), 23.71 (CB), 24.00 (C5), 25.01 (C4), 36.57 (C3), 53.16 (C6), 54.64 ($O\underline{C}H_3$), 59.87 (C2), 60.66 (C8), 64.09 (CA), 65.52 (C9), 99.57 (C17), 116.72 (C11), 118.65 (q, 321.84 Hz, $\underline{C}F_3$), 119.17 (C19), 120.45 (C14), 124.52 (C16), 130.75 (C20), 135.35 (C10), 141.95 (C21), 142.83 (C15), 146.31 (C13), 157.48 (C18). ^{19}F-NMR (300 MHz, $CDCl_3$): δ: -79.35. IR (KBr Disc): $\overline{\nu}$ (cm^{-1}) = 3453 (OH), 2969 (CH), 2918 (CH), 2883 (CH), 2849 (CH), 1625 (alkene C=C), 1593 (C=N), 1558, 1512 (aromatic C=C), 1475, 1434, 1418, 1352, 1327, 1229, 1199 (C-O), 1137, 1056, 829, 739, 617, 570, 514.

2.7.5. Synthesis of 1-N-hexyl quininium iodide: [C_6Qn][I] (3a)

Quinine (1.29 g, 3.99 mmol) was suspended in MeCN (8 mL). To this was added hexyl iodide (1.09 g 5.14 mmol). The suspension was stirred and heated to 80 °C so that the quinine dissolved. During the first 20 minutes the solution became orange. The total reaction time was 23 hours. Solvent was removed by rotary evaporation to leave a brown solid. This was stirred vigorously with cyclohexane (2 x 10 mL) for 20 minutes and then the solid filtered off each time. The solid was recrystallized from boiling methanol (~ 0.6 mL). The precipitate which formed at room temperature was washed with a small amount of cold methanol and then diethyl ether. The solid obtained was dried overnight on high vacuum. [C_6Qn][I] (**3a**) yield = 1.37 g, 2.55 mmol, 64 %.

Quinine (1.48 g, 4.57 mmol) was dissolved in Me-THF (45 mL). To this was added iodohexane (0.96 g, 4.50 mmol). The mixture was stirred and heated to reflux for 18 hours, during which time a white precipitate formed in a purple solution. The reaction was filtered under gravity and washed with a small amount of Me-THF. The solid was dried under high vacuum overnight. [C_6Qn][I] (**3a**) yield = 0.713 g, 1.33 mmol, 29.5 %.

ESI-MS *m/z*: Found 409.2697 (M^+), calcd. for $C_{26}H_{37}N_2O_2$: 409.2844. Found 945.4755. ($M^+ + M^+ + M^-$), calcd. for $(C_{26}H_{37}N_2O_2)_2I$: 945.4744.

^{1}H-NMR (300 MHz, $CDCl_3$): δ: 0.85 (t, 7.16 Hz, 3H, HF), 1.25-1.41 (m, 5H, HE, HD, H5_{endo}), 1.49-1.59 (m, 2H, HC), 1.80-2.00 (m, 4H, HB, H7_{endo}, H5_{exo}), 2.12-2.23 (m, 2H, H6_{endo}, H4), 2.79-2.86 (m, H, H3), 2.97-3.04 (m, H, H7_{exo}), 3.38-3.44 (m, H, H2), 3.59-3.68 (m, H, H2′), 3.86-3.94 (m, 2H, HA), 3.90 (s, 3H, OC$\underline{H}_3$), 4.04-4.14 (m, H, H6_{exo}), 4.50-4.57 (m, H, H8), 4.98-5.05 (m, 2H, H11, H11′), 5.33 (d, 6.03 Hz, H, H9), 5.45-5.56 (m, H, H10), 6.43 (d, 6.22 Hz, H, O$\underline{H}$), 7.06 (d, 2.45 Hz, H, H19), 7.35 (dd, 2.64 Hz, 9.23 Hz, H, H14), 7.65 (d, 4.33 Hz, H, H17), 8.00 (d, 9.23 Hz, H, H20), 8.69 (d, 4.52 Hz, H, H13). ^{13}C-NMR (300 MHz, $CDCl_3$): δ: 13.03 (CF), 20.27 (CE), 21.49 (C7), 22.16 (CD), 24.03 (CC), 25.19 (C5), 25.42 (C4), 30.48 (CB), 36.66 (C3), 53.18 (C6), 55.17 (O$\underline{C}H_3$), 60.17 (C2), 60.78 (C8), 62.40 (CA), 65.96 (C9), 100.72 (C17), 116.94 (C11), 119.69 (C19), 119.72 (C14), 124.67 (C16), 131.28 (C20), 135.46 (C10), 142.04 (C21), 143.21 (C15), 146.72 (C13), 157.22 (C18).

2.7.6. Synthesis of 1-N-hexyl quininium bistriflimide: [C_6Qn][NTf_2] (3c)

1-*N*-hexyl quininium iodide, [C_6Qn][I] (**3a**) (0.43 g, 0.8 mmol) was dissolved in acetone (3 mL). To this was added Li(NTf_2) (0.36 g, 1.25 mmol) in acetone (4 mL). The reaction was heated to 60 °C for 4 hours. The reaction was concentrated to half its volume and a further portion of Li(NTf_2) (0.13 g, 0.45 mmol) was added. The reaction was stirred overnight. The solvent was removed by rotary evaporation to leave a red-brown oil which solidified on standing. The solid was heated to 60 °C and washed with deionised water (3 x 5 mL) with vigorous stirring. DCM (5 mL) was added and the layers were separated. The aqueous layers were combined and washed with DCM (2 x 5 mL) and the combined organic layers were removed by rotary evaporation to leave a dark purple solid liquid which became glassy when cooled. The material was dried overnight under high vacuum at 60 °C, during which time it was a liquid. The purple liquid again became a partially crystalline glass upon cooling. [C_6Qn][NTf_2] (**3c**) yield = 0.54 g, 0.788 mmol, 98.5 %.

Found C 48.63, H 5.25, N 5.98 S 8.88. Calcd. For $C_{28}H_{37}F_6N_3O_6S_2$: C 48.76, H 5.41, N 6.09 S 9.30 %. ESI-MS *m/z*: Found 409.2704 (M^+), calcd. for $C_{26}H_{37}N_2O_2$: 409.2844. Found 279.9173 (M^-), calcd. for $C_2F_6NO_4S_2$: 279.9173. TGA = 217 °C. m.p. < 45 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ: 0.83 (t, 7.15 Hz, 3H, HF), 1.24-1.33 (m, 5H, HE, HD, H5_{endo}), 1.40-1.47 (m, 2H, HC), 1.78-1.95 (m, 3H, HB, H7_{endo}), 2.01-2.02 (m, H, H5_{exo}), 2.08-2.28 (m, 2H, H6_{endo}, H4), 2.77 (br s, H, H3), 2.97-3.01 (m, H, H7_{exo}), 3.29-3.50 (m, 2H, H2), 3.46-3.67 (m, 3H, H6_{exo}, HA), 3.85 (s, 3H, OC$\underline{H}_3$), 4.24-4.31 (m, H, H8), 4.88 (d, 3.48 Hz, H, H9), 4.97-5.03 (m, 2H, H11, H11′), 5.41-5.52 (m, H, H10), 6.18 (s, H, O$\underline{H}$), 6.93 (d, 2.57 Hz, H, H19), 7.34 (dd, 2.57 Hz, 9.35 Hz, H, H14), 7.62 (d, 4.77 Hz, H, H17), 7.96 (d, 9.35 Hz, H, H20), 8.63 (d, 4.59 Hz, H, H13). ^{13}C-NMR (300 MHz, $CDCl_3$): δ: 12.76 (CF), 19.82 (CE), 21.34 (C7), 21.94 (CD), 24.02 (CC), 25.06 (C5), 25.12 (C4), 30.19 (CB), 36.72 (C3), 53.13(C6), 54.67 (O$\underline{C}H_3$), 60.20 (C2), 60.73 (C8), 63.90 (CA), 65.88 (C9), 99.77 (C17), 117.00 (C11), 118.60 (q, 321.84 Hz, $\underline{C}F_3$), 119.10 (C19), 120.15 (C14), 124.44 (C16), 131.12 (C20), 135.21 (C10), 141.67 (C21), 143.05 (C15), 146.31 (C13), 157.44 (C18). ^{19}F-NMR (300 MHz, $CDCl_3$): δ: -78.78. IR (KBr Disc): $\bar{\nu}$ (cm^{-1}) = 3493 (OH), 2961 (CH), 1627 (alkene C=C), 1593 (C=N), 1512 (aromatic C=C), 1475, 1435, 1351, 1195 (C-O), 1135, 1057, 827, 787, 741 617, 570, 513.

2.7.7. Synthesis of 1-N-octyl quininium bromide: [C_8Qn][Br] (4b)

Quinine (1.00 g, 3.08 mmol) was suspended in Me-THF (9 mL). To this was added octyl bromide (0.60 g, 3.09 mmol) dissolved in Me-THF (6 mL). A condenser was fitted and the mixture heated to reflux so that a colourless solution formed. The reaction was continued overnight and an orange precipitate formed. The precipitate was separated by vacuum filtration and washed with Me-THF and diethyl ether to leave a white solid. The solid was dried by suction and then overnight under high vacuum. Yield [C_8Qn][Br] (**4b**) = 0.92 g, 1.77 mmol, 57.3 %.

ESI-MS *m/z*: Found 437.2888 (M^+), calcd. for $C_{28}H_{41}N_2O_2$: 437.3157. Found 955.5096 ($M^+ + M^+ + M^-$), calcd. for $(C_{28}H_{41}N_2O_2)_2Br$: 953.5508.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.88 (t, 6.24 Hz, 3H, HH), 1.29-1.38 (m, 11H, HG-HC, $H5_{endo}$), 1.84-1.94 (m, 3H, HB, $H7_{endo}$), 2.02 (br s, H, $H5_{exo}$), 2.12-2.21 (m, 2H, $H6_{endo}$, H4), 2.74-2.83 (m, H, H3), 3.41-3.65 (m, 3H, HA, $H7_{exo}$), 3.73-3.79 (m, 3H, H2, $H6_{exo}$), 3.90-4.00 (m, 4H, H8, $OC\underline{H_3}$), 5.00-5.16 (m, 2H, H11, H11′), 5.71-5.83 (m, H, H10), 6.26 (br s, H, $O\underline{H}$), 6.52 (d, 3.30 Hz, H, H9), 7.26 (s, H, H19), 7.50 (d, 11.19 Hz, H, H17), 7.71 (d, 4.03 Hz, H, H14), 8.01 (d, 9.35 Hz, H, H20), 8.80 (d, 4.40 Hz, H, H13). ^{13}C-NMR (300 MHz, DMSO-d_6): 14.37 (CH), 20.43 (CG), 22.35 (C7), 22.46 (CF), 25.00 (C5), 26.31 (C4), 26.60 (CE), 28.90 (CD), 28.93 (CC), 31.60 (CB), 37.91 (C3), 52.55 (C6), 55.84 ($O\underline{C}H_3$), 59.89 (C2), 60.29 (C8), 64.16 (CA), 66.60 (C9), 102.49 (C17), 116.96 (C11), 120.67 (C19), 121.72 (C14), 125.73 (C16), 131.87 (C20), 138.41 (C10), 144.08 (C21), 144.50 (C15), 147.89 (C13), 157.70 (C18).

2.7.8. Synthesis of 1-N-octyl quininium bistriflimide: [C_8Qn][NTf_2] (4c)

1-*N*-octyl quininium bromide, [C_8Qn][I] (**4b**) (0.23 g, 0.444 mmol), was dissolved in acetone (7 mL). To this was added Li(NTf_2) (0.26 g, 0.888 mmol). The reaction was stirred and heated to reflux for 17 hours. Solvent was removed by rotary evaporation to leave a white solid. The solid was dissolved in DCM (4 mL) and heated to reflux with deionised water (3 x 4 mL). The layers were separated and the aqueous layers were extracted with DCM (2 x 3 mL). The organic layers were combined and solvent removed by rotary evaporation. The white solid was dried under high vacuum overnight. Yield [C_8Qn][NTf_2] (**4c**) = 0.29 g, 0.406 mmol, 91.5 %.

Found C 50.20, H 6.13, N 5.96, S 8.93. Calcd. for $C_{30}H_{41}F_6N_3O_6S_2$: C 50.20, H 5.76, N, 5.85, S 8.93 %. ESI-MS *m/z*: Found 437.2823 (M^+), calcd. for $C_{28}H_{41}N_2O_2$: 437.3157. Found 279.8977 (M^-), calcd. for $C_2F_6NO_4S_2$: 279.9173. TGA = 240 °C. m.p. = 122.17 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.94 (t, 7.02 Hz, 3H, HH), 1.34-1.44 (m, 11H, HG-HC, $H5_{endo}$), 1.88-1.99 (m, 3H, HB, $H7_{endo}$), 2.07 (br s, H, $H5_{exo}$), 2.17-2.22 (m, 2H, $H6_{endo}$, H4), 2.79-2.87 (m, H, H3), 3.45-3.67 (m, 3H, HA, $H7_{exo}$), 3.76-3.83 (m, 3H, H2, $H6_{exo}$), 3.96-3.99 (m, H, H8), 4.05 (s, 3H, $OC\underline{H_3}$), 5.06-5.22 (m, 2H, H11, H11'), 5.76-5.88 (m, H, H10), 6.30 (br s, H, $O\underline{H}$), 6.56 (d, 3.22 Hz, H, H9), 7.31 (d, 2.34 Hz, H, H19), 7.55 (dd, 2.34 Hz, 9.06 Hz, H, H17), 7.77 (d, 4.38 Hz, H, H14), 8.07 (d, 9.35 Hz, H, H20), 8.76 (d, 4.38 Hz, H, H13). ^{13}C-NMR (300 MHz, DMSO-d_6): 14.33 (CH), 20.25 (CG), 22.35 (C7), 22.46 (CF), 25.00 (C5), 26.30 (C4), 26.60 (CE), 28.90 (CD), 28.93 (CC), 31.60 (CB), 37.92 (C3), 52.56 (C6), 55.78 ($O\underline{C}H_3$), 59.91 (C2), 60.30 (C8), 64.25 (CA), 66.64 (C9), 102.45 (C17), 116.96 (C11), 119.87 (d, 322.99 Hz, $\underline{C}F_3$), 120.66 (C19), 121.68 (C14), 125.70 (C16), 131.90 (C20), 138.38 (C10), 144.09 (C21), 144.47 (C15), 147.89 (C13), 157.70 (C18). ^{19}F-NMR (300 MHz, DMSO-d_6): -79.14. δ: IR (KBr Disc): $\bar{\nu}$ (cm^{-1}) = 3476 (OH), 2960 (CH), 2930 (CH), 2860 (CH), 1622 (aromatic C=C), 1593 (C=N), 1510 (aromatic C=C), 1475, 1432, 1353, 1194 (C-O), 1139, 1052, 917, 827, 797, 741, 621, 570, 514.

2.7.9. Synthesis of 1-N-ethyl methylether quininium bromide: [C_1OC_2Qn][Br] (5b)

Quinine (1.30 g, 4.01 mmol) was dissolved in Me-THF (25 mL), 2-bromoethyl methyl ether (0.53 g, 3.79 mmol) was added to the stirred solution. The mixture was heated to 90 °C for 21 hours during which time a purple solution formed. Upon cooling the reaction mixture gelled. The gel was broken up and stirred vigorously forming a solution and a precipitate. The precipitate was filtered and washed with a small amount of Me-THF to leave a pale pink solid that was dried by rotary evaporation. MeTHF remained in the product. This was carried through to the next step and then removed. Me-THF peaks from spectrum S9.1, S9.2 and S9.3 are underlined in analysis below. Crude yield [C_1OC_2Qn][Br] (**5b**) = 0.18 g, 0.399 mmol, 10.0 %.

ESI-MS *m/z*: Found 383.2256 (M^+), calcd. for $C_{23}H_{31}N_2O_3$: 383.2324. Found 847.3843 ($M^+ + M^+ + M^-$), calcd. for $(C_{23}H_{31}N_2O_3)_2Br$: 846.3842.

^{1}H-NMR (300 MHz, $CDCl_3$): δ: 1.38-1.47 (m, H, $H5_{endo}$), 1.96-2.03 (m, H, $H7_{endo}$), 2.05-2.08 (m, H, $H5_{exo}$), 2.13-2.20 (m, H, $H6_{endo}$), 2.25-2.35 (m, H, H4), 2.80-2.87 (m, H, H3), 3.23-3.29 (m, H, $H7_{exo}$), 3.43 (s, 3H, HC), 3.66-3.70 (m, H, $H6_{exo}$), 3.86-3.97 (m, 2H, HB), 3.99 (s, 3H, $OC\underline{H_3}$), 4.04-4.16 (m, 2H, HA), 4.29-4.37 (m, H, H2), 4.49-4.55 (m, H, H2′), 4.78-4.86 (m, H, H8) 5.07-5.13 (m, 2H, H11, H11'), 5.54-5.65 (m, H, H10), 6.19 (d, 6.42 Hz, H, $O\underline{H}$), 6.45 (d, 5.69 Hz, H, H9), 7.33 (d, 2.57 Hz, H, H19), 7.40 (dd, 2.57 Hz, 9.17 Hz, H, H17), 7.70 (d, 4.40 Hz, H, H14), 8.06 (d, 9.17 Hz, H, H20), 8.76 (d, 4.58 Hz, H, H13). Me-THF = 1.23 (d, 6.05 Hz), 1.83-1.88 (m), 3.72-3.78 (m). ^{13}C-NMR (300 MHz, DMSO-d_6): δ: 20.61 (C7), 25.06 (C5), 26.28 (C4), 37.94 (C3), 53.51 (C6), 56.04 ($O\underline{C}H_3$), 58.54 (CC), 60.06 (CB), 60.82 (CA), 64.41 (C2), 65.41 (C8), 67.05 (C9), 102.79 (C17), 116.99 (C11), 120.63 (C19), 121.65 (C14), 125.87 (C16), 131.81 (C20), 138.44 (C10), 144.11 (C21), 144.37 (C15), 147.84 (C13), 157.74 (C18). Me-THF at 21.31, 25.50, 33.09, 67.39.

2.7.10. Synthesis of 1-N-ethyl methylether quininium bistriflimide: [C_1OC_2Qn][NTf_2] (5c)

1-*N*-ethyl methylether quininium bromide, [C_1OC_2Qn][Br] (**5b**) (0.1726 g, 0.372 mmol) was dissolved in methanol (5 mL). To this was added Li(NTf_2) (0.19 g, 0.651 mmol). The reaction was heated to 60 °C and stirred for 19 h. The solvent was removed by rotary evaporation to leave an orange solid. The solid was dissolved in DCM (3 mL) and heated to reflux with deionised water (3 x 3 mL) for 30 minutes, water was decanted after each reflux. The layers were separated in a funnel and organic solvent removed by rotary evaporation. The orange solid was dried overnight under high vacuum. Yield [C_1OC_2Qn][NTf_2] (**5c**) = 0.20 g, 0.303 mmol, 81.5 %.

Found C 45.52, H 4.74, N 6.25, S 9.23. Calcd. for $C_{25}H_{31}F_6N_3O_7S_2$: C 45.24, H 4.71, N 6.33, S 9.23 %. ESI-MS *m/z*: 383.2367 (M^+), calcd. for $C_{23}H_{31}N_2O_3$: 383.2324. Found 279.9173 (M^-), calcd. for $C_2F_6NO_4S_2$: 279.9173. TGA = 207 °C. m.p. = 124 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ: 1.40-1.48 (m, H, $H5_{endo}$), 1.94-2.01 (m, H, $H7_{endo}$), 2.07 (m, H, $H5_{exo}$), 2.15-2.26 (m, 2H, $H6_{endo}$, H4), 2.82-2.90 (m, H, H3), 3.39 (s, 3H, HC) 3.52-3.69 (m, 3H, $H7_{exo}$, H2), 3.85-3.95 (m, 3H, $H6_{exo}$, HB), 4.02-4.04 (m, 3H, HA, H8), 4.07 (s, 3H, $OC\underline{H_3}$), 5.06-5.22 (m, 2H, H11, H11'), 5.77-5.89 (m, H, H10), 6.29 (d, 3.12 Hz, H, $O\underline{H}$), 6.62 (d, 3.48 Hz, H, H9), 7.35 (d, 2.38 Hz, H, H19), 7.55 (dd, 2.38 Hz, 9.17 Hz, H, H17), 7.75 (d, 4.40 Hz, H, H14), 8.07 (d, 9.17 Hz, H, H20), 8.85 (d, 4.58 Hz, H, H13). ^{13}C-NMR (300 MHz, DMSO-d_6): δ: 20.67 (C7), 25.08 (C5), 26.27 (C4), 37.94 (C3), 53.52 (C6), 55.98 ($O\underline{C}H_3$), 58.52 (CC), 60.04 (CB), 60.82 (CA), 64.48 (C2), 65.39 (C8), 67.07 (C9), 102.75 (C17), 116.99 (C11), 120.63 (C19), 121.60 (C14), 125.82 (C16), 131.83 (C20), 138.39 (C10), 144.09 (C21), 144.34 (C15), 147.84 (C13), 157.74 (C18), $\underline{C}F_3$ not visible. ^{19}F-NMR (300 MHz, DMSO-d_6): δ: -78.72. IR (KBr Disc): $\bar{\nu}$ (cm^{-1}) = 3066 (OH), 3003 (CH), 2962 (CH), 1625 (alkene C=C), 1511 (C=N), 1471 (aromatic C=C), 1345, 1320 1187 (C-O), 1139, 1059, 1032, 833, 601, 571.

2.7.11. Synthesis of 1-N-2-(2-methoxyethoxy)ethane quininium bromide: [$C_1OC_2OC_2Qn$][Br] (6b)

Quinine (1.4767 g, 4.55 mmol), was dissolved in Me-THF (30 mL). To this was added 1-bromo-2-(2-methoxyethoxy)ethane (0.7802 g, 4.26 mmol). The reaction was heated to 93 °C and stirred for 20 hours. A purple solution with some purple precipitate had formed. The precipitate was separated by filtration and washed with Me-THF and diethyl ether before drying overnight under high vacuum. The filtrate was concentrated by rotary evaporation and formed a gel on cooling. Yield $[C_1OC_2OC_2Qn][Br]$ (**6b**) = 0.44 g, 0.866 mmol, 19.0 %.

ESI-MS *m/z*: Found 427.2540 (M^+), calcd. for $C_{25}H_{35}N_2O_4$: 427.2586. Found 935.4370 ($M^+ + M^+ + M^-$), calcd. for $(C_{25}H_{35}N_2O_4)_2Br$: 935.4366.

^{1}H-NMR (300 MHz, DMSO-d_6): δ: 1.42-1.50 (m, H, $H5_{endo}$), 1.89-1.97 (m, H, $H7_{endo}$), 2.02-2.03 (m, H, $H5_{exo}$), 2.13-2.18 (m, 2H, $H6_{endo}$, H4), 2.79-2.86 (m, H, H3), 3.17 (s, 3H, HE), 3.35-3.37 (m, 2H, HD), 3.51-3.65 (m, 4H, HC, HB), 3.84-3.97 (m, 3H, $H7_{exo}$, H2), 4.02-4.05 (m, 7H, $OC\underline{H}_3$, HA, $H6_{exo}$, H8), 5.02-5.18 (m, 2H, H11, H11'), 5.75-5.86 (m, H, H10), 6.25 (d, 3.85 Hz, H, $O\underline{H}$), 6.56 (d, 4.22 Hz, H, H9), 7.35 (d, 2.57 Hz, H, H19), 7.48 (dd, 2.57 Hz, 9.17 Hz, H, H17), 7.67 (d, 4.59 Hz, H, H14), 8.00 (d, 9.17 Hz, H, H20), 8.79 (d, 4.40 Hz, H, H13). ^{13}C-NMR (400 MHz, DMSO-d_6): δ: 20.66 (C7), 25.05 (C5), 26.31 (C4), 37.97 (C3), 53.40 (C6), 56.11 ($O\underline{C}H_3$), 58.38 (CE), 60.15 (CD), 60.84 (CC), 63.93 (C2), 64.39 (C8), 67.13 (C9), 69.77 (CB), 71.24 (CA), 102.80 (C17), 116.96 (C11), 120.54 (C19), 121.74 (C14), 126.02 (C16), 131.77 (C20), 138.44 (C10), 144.15 (C21), 144.37 (C15), 147.80 (C13), 157.74 (C18).

2.7.12. Synthesis of 1-N-2-(2-methoxyethoxy)ethane quininium bistriflimide: $[C_1OC_2OC_2Qn][NTf_2]$ (6c)

1-*N*-2-(2-methoxyethoxy)ethane quininium bromide, $[C_1OC_2OC_2Qn][Br]$ (**6b**) (0.44 g, 0.866 mmol) was dissolved in acetone (3 mL). To this was added $Li(NTf_2)$ (0.41 g, 1.42 mmol). The brown solution was heated to 70 °C with stirring for 17 hours. Solvent was removed by rotary evaporation to leave a viscous brown liquid which solidified upon cooling. The solid was dissolved in DCM (3 mL) and refluxed three times with deionised water (3 x 5 mL) with water decanted after each reflux. Layers were separated in a funnel and the organic solvent was removed by rotary evaporation to leave a viscous liquid. The liquid was dried overnight under high vacuum. Yield $[C_1OC_2OC_2Qn][NTf_2]$ (**6c**) = 0.56 g, 0.786 mmol), 90.7 %.

Found C 46.88, H 4.91, N 6.80, S 8.28. Calcd. for $C_{27}H_{35}F_6N_3O_6S_2$: C 45.82, H 4.98, N, 5.94, S 9.06 %. ESI-Ms *m/z*: Found 427.2278 (M^+), calcd. for $C_{25}H_{35}N_2O_4$: 427.2586. Found 279.9173 (M^-), calcd. for $C_{25}H_{35}N_2O_4$: 279.9173. TGA = 212 °C. T_g = -8 °C. T_m not observed.

^{1}H-NMR (300 MHz, DMSO-d_6): δ: 1.44-1.52 (m, H, $H5_{endo}$), 1.94-2.01 (m, H, $H7_{endo}$), 2.08 (br s, H, $H5_{exo}$), 2.18-2.34 (m, 2H, $H6_{endo}$, H4), 2.83-2.90 (m, H, H3), 3.25 (s, 3H, HE), 3.44-3.46 (m, 2H, HD), 3.54-3.68 (m, 4H, HC, HB), 3.87-3.99 (m, 3H, $H7_{exo}$, H2), 4.07-4.10 (m, 7H, $OC\underline{H}_3$, HA, $H6_{exo}$, H8), 5.08-5.23 (m, 2H, H11, H11'), 5.79-5.90 (m, H, H10), 6.29 (br s, H, $O\underline{H}$), 6.61 (d, 3.12 Hz, H, H9), 7.37 (br s, H, H19), 7.55 (d, 10.09 Hz, H, H17), 7.74 (d, 4.03 Hz, H, H14), 8.07 (d, 9.17 Hz, H, H20) 8.86 (d, 4.22 Hz, H, H13). ^{13}C-NMR (400 MHz, DMSO-d_6): δ: 20.55 (C7), 25.06 (C5), 26.27 (C4), 37.95 (C3), 53.43 (C6), 55.98 ($O\underline{C}H_3$), 58.40 (CE), 60.09 (CD), 60.82 (CC), 63.93 (C2), 64.47 (C8), 67.16 (C9), 69.78 (CB), 71.28 (CA), 102.74 (C17), 116.96 (C11), 119.87 (d, 321.84 Hz, $\underline{C}F_3$) 120.54 (C19), 121.66 (C14), 125.90 (C16), 131.81 (C20), 138.39 (C10), 144.12 (C21), 144.31 (C15), 147.81 (C13), 157.74 (C18). ^{19}F-NMR (300 MHz, DMSO-d_6): δ: -79.73. IR (Neat): $\bar{\nu}$ (cm^{-1}) = 3192 (OH), 3082 (CH), 2937 (CH), 1622 (alkene C=C), 1560 (C=N), 1512 (aromatic C=C), 1462, 1433, 1357, 1232 (C-O), 1134, 1057, 934, 829, 790, 655, 571.

2.8. Knoevenagel condensation

2.8.1. General Procedure for Knoevenagel condensation demonstrated for [C_4Qn][NTf_2] (2c) (Table 3, entry 3). Adapted from Keithellakpam *et al.* [25].

Malononitrile (68.2 mg, 1.03 mmol) was added to a 10 mL round bottomed flask. To this was added benzaldehyde (0.10 g, 1.0 mmol) and DCM (0.18 g) and the flask capped and sealed. The mixture was briefly stirred to ensure it was homogeneous. Then [C_4Qn][NTf_2] (**2c**) (64.4 mg, 0.01 mmol, 0.1 mol eq.) was added, the total mass recorded, and the flask was capped, sealed and stirred at 500 RPM for 1 hour. After this time a reaction sample of known mass (0.3032 g) was taken. To this sample was added ethyl trifluoroacetate (0.3149g, 6.13 mmol, 1:1 wt/wt.). $CDCl_3$ (0.4 mL) was added and a ^{1}H NMR spectrum was recorded (ESI, Spectrum S13). The ethyl trifluoroacetate $C\underline{H_3}$ triplet at 1.26 ppm was monitored. Integration was set to 3 for 3H (ESI, Spectrum S13). The PhC$\underline{H}$ singlet of the product was monitored at 7.73 ppm. Integration was measured as 0.29 (ESI, Spectrum S13). The solution yield was calculated as detailed in section 2 of the ESI.

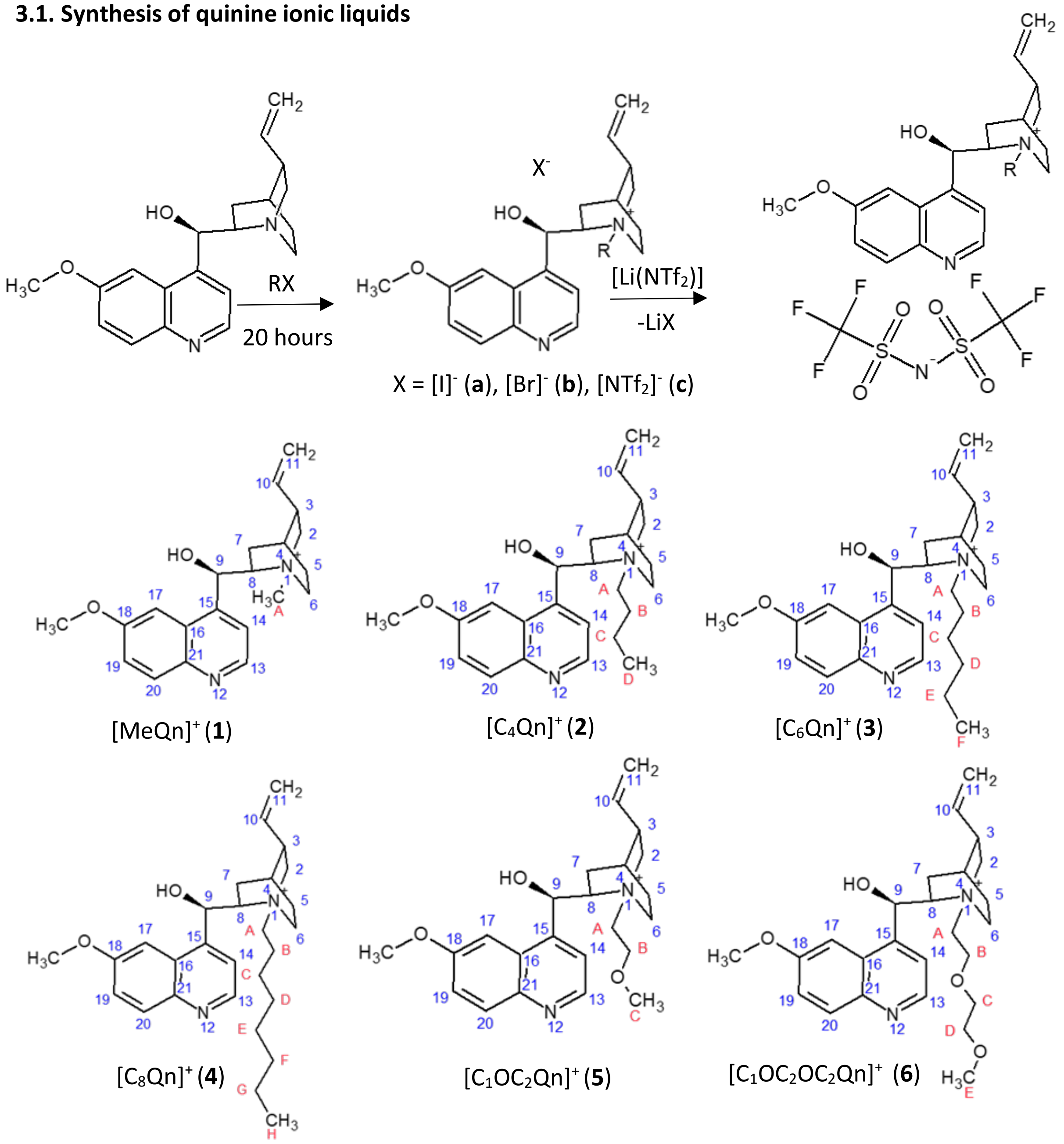
2.8.2. Recycle of [MeQn][NTf_2] (1c)

Malononitrile (55.9 mg, 0.85 mmol, 1 eq.) was added to a 10 mL round bottomed flask. To this was added benzaldehyde (81.9 mg, 0.77 mmol, 1 eq.) and DCM (0.13 g) and the flask capped and sealed. The mixture was briefly stirred to ensure it was homogeneous. Then [MeQn][NTf_2] (**1c**) (48.1 mg, 0.008 mmol, 0.1 eq.) was added, the total mass recorded, and the flask was capped, sealed and stirred at 500 RPM for 30 minutes. After this time a reaction sample of known mass (0.0242 g) was taken. To this sample was added ethyl trifluoroacetate (0.0111 g, 0.071 mmol). $CDCl_3$ (0.4 mL) was added and a ^{1}H NMR spectrum was recorded.

DCM was removed from the remaining reaction mixture *via* rotary evaporation to leave a yellow solid. The solid was suspended in diethyl ether (3 mL). This was filtered and the solid residue washed with diethyl ether (2 x 3 mL) to leave a white solid. This was dried *via* rotary evaporation to leave 39.5 mg of recovered [MeQn][NTf_2] (**1c**). The recovered [MeQn][NTf_2] (**1c**) was reused twice more, with the reaction procedure and recovery identical to that outlined above. ^{1}H NMR of the recovered catalyst showed no reaction products (ESI Spectrum S14) and ^{1}H NMR of the evaporated filtrate showed no [MeQn][NTf_2] (ESI Spectrum S15).

3. Results and discussion

3.1. Synthesis of quinine ionic liquids



X = [I]$^-$ (**a**), [Br]$^-$ (**b**), [NTf$_2$]$^-$ (**c**)

[MeQn]$^+$ (**1**)

[C$_4$Qn]$^+$ (**2**)

[C$_6$Qn]$^+$ (**3**)

[C$_8$Qn]$^+$ (**4**)

[C$_1$OC$_2$Qn]$^+$ (**5**)

[C$_1$OC$_2$OC$_2$Qn]$^+$ (**6**)

Figure 1: General for synthesis of quinine ionic liquids from quinine, structures of ionic liquids.

A general reaction scheme for quinine ionic liquid synthesis and the structures of the cations is given in Figure 1. The synthesis follows the procedure of Berkessel *et. al.* [24]. Quinine was reacted with 1 molar equivalent of alkyl halide in either methanol or acetonitrile. Following this, an ion exchange using [Li(NTf$_2$)] was performed. [MeQn][I] (**1a**) was synthesised in almost quantitative yield in methanol following recrystallisation in boiling methanol. This method was not successful for the other quinine halides, which were not readily recrystallised. Changing the solvent to 2-methyltetrahydrofuran (Me-THF) caused precipitation of the quinine halide which could be obtained pure after filtration and washing with Me-THF and diethyl ether. This method was used to prepare the remaining quinine halides (**2a, 3a, 4b, 5b, 6b**) and has the added advantage that Me-THF is a 'green' solvent, which can be obtained from renewable sources [26]. This builds on the green approach of using quinine as a starting material in order to synthesise green and sustainable basic ionic liquids. Synthesis of the halide salt was low yielding for the ether quinine ionic liquids $[C_1OC_2Qn][NTf_2]$ (**5c**) and $[C_1OC_2Qn][NTf_2]$ (**6c**). All ion exchange reactions yielded greater than 80 %.

3.2. Physical properties of quinine ionic liquids

Table 1: Thermal properties and Hammett basicity of quinine ionic liquids.

Entry	Quinine Ionic Liquid	$T_{melting}$ / °C[a]	$T_{degradation}$ / °C[b]	Hammett Basicity (H_)[f]
1	$[MeQn][NTf_2]$ (**1c**)	131	263	8.51
2	$[C_4Qn][NTf_2]$ (**2c**)	107	224	8.65
3	$[C_6Qn][NTf_2]$ (**3c**)	< 45,[c] (11)[d]	217	9.40
4	$[C_8Qn][NTf_2]$ (**4c**)	122	240	8.44
5	$[C_1OC_2Qn][NTf_2]$ (**5c**)	124 (10)[d]	207	8.72
6	$[C_1OC_2OC_2Qn][NTf_2]$ (**6c**)	< RT,[e] (- 8)[d]	213	9.95

[a] Melting point measured by dye sensitised calorimetry. **[b]** Degradation onset temperature measured by thermogravimetric analysis. [c] Visual observation. [d] Glass transition temperature. [e] No melting point observed by DSC. [f] Determined by monitoring UV absorbance at 595 nm of a 0.09 mM solution of IL in methanolic bromophenol blue.

The thermal properties and Hammett basicity functions of the quinine ionic liquids are shown in Table 1. The range of cation structures allows for assessment of the effect of the alkyl chain composition on physical properties and catalysis. Water is not influencing the properties as Karl Fischer titration showed <0.1 wt. % in all ionic liquids. The determination of the pH of an ionic liquid is not straightforward when it is insoluble or unstable in water. The Hammett function (H_0) has been used as a measure of the acidity of non-aqueous Brønsted acid systems [27,28], and has more recently been used to determine basicity in non-aqueous systems [29,30]. The Hammett basicity (H_) of the quinine ionic liquids was measured by monitoring the UV absorbance of methanolic bromophenol blue at a fixed concentration of ionic liquid.

The melting point behaviour of the quinine salts was found to vary significantly as the additional functional group was changed (Table 1). The high melting points (above 100 °C), for several of the salts can be partly attributed to hydrogen bonding involving the hydroxyl group of the cation. SPARTAN calculations performed on $[MeQn][NTf_2]$ (**1c**) (ESI Section 8) [31] show hydrogen bonding interactions between this hydroxyl group and the anion. However, solving the structure of $[C_4Qn][NTf_2]$ (**2c**) as a two-component twin by X-ray crystallography (Cambridge database CCDC = 1920034) shows, that in the solid crystalline state, hydrogen bonds form between the hydroxyl group and the free nitrogen atom of neighbouring cations (Figure 2, Figure 3, Table 2).

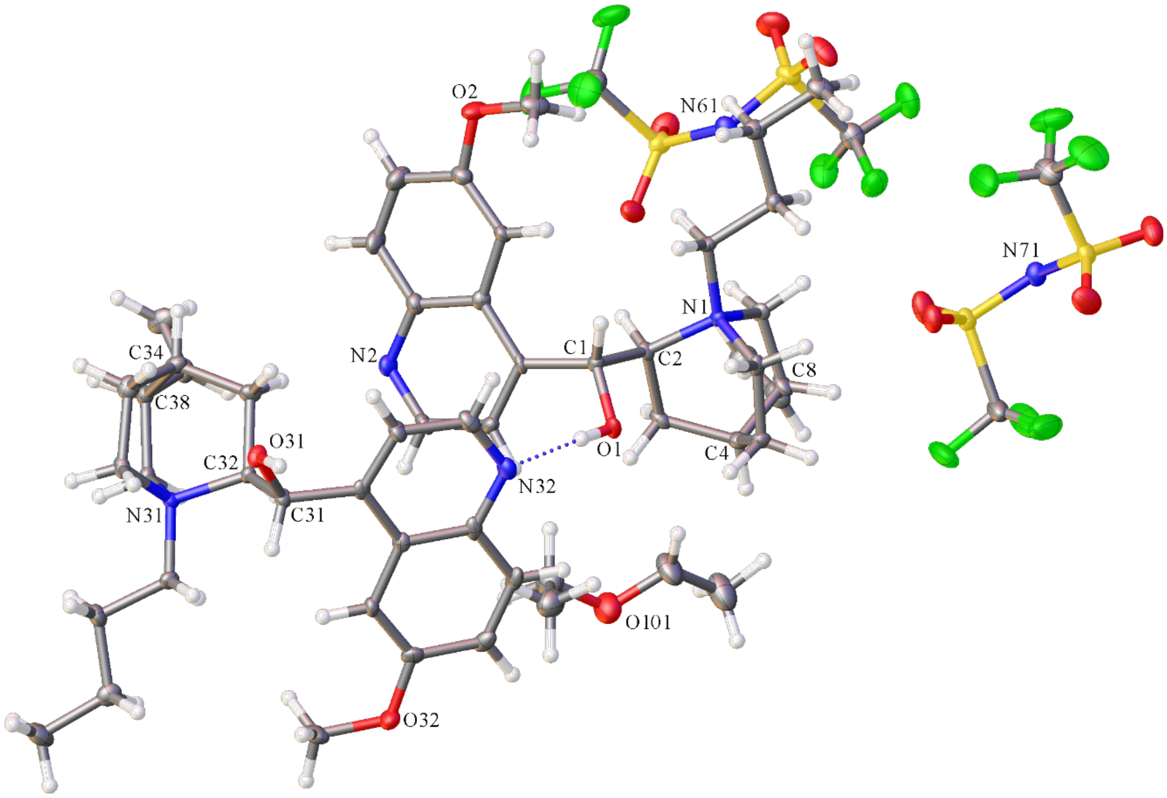


Figure 2: Crystal structure of [C_4Qn][NTf_2] (**2c**).

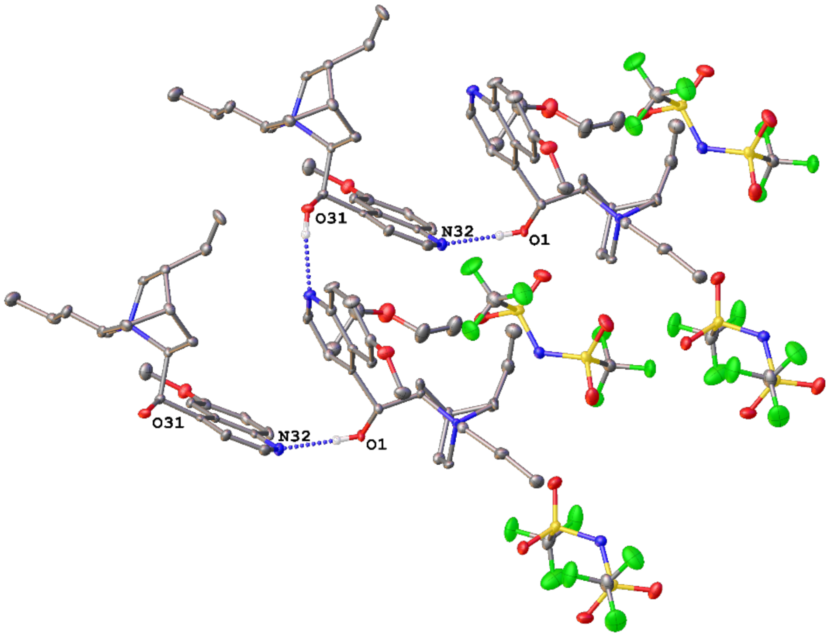


Figure 3: The following hydrogen bonding interactions with a maximum D-D distance of 2.9 Å and a minimum angle of 120 ˚ are present in [C_4Qn][NTf_2] (**2c**): O1–N32: 2.774 Å, O31–N2_1: 2.817 Å.

Table 2: Hydrogen bond information for [C_4Qn][NTf_2] (**2c**).

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
O1	H1	N32	0.84	1.93	2.774(5)	176.6
O31	H31	N2^{1}	0.84	1.98	2.817(5)	171.5

Symmetry factor: -1+x,+y,+z

The alkyl quinine ionic liquids (**1c, 2c, 3c, 4c**) (Table 1 entries 1-4) show decreasing melting point as the chain length increases from 1 to 6 carbon atoms before the trend reverses when the chain length is 8. Conventional wisdom suggests that initial increases in chain length will prevent stacking of the ions and lower the melting point [1]. The packing diagram obtained from X-ray crystallography supports this model (Figure 4). In [C_4Qn][NTf_2] (**2c**) crystals the butyl chain of one cation points towards the adjacent cation. As the chain length increases it is expected that the cations will be forced further apart, which will decrease interactions between them and decrease the melting point. Crystal structures of the long chain quinine ionic liquids were not obtained as these salts exhibited a glassy state and could not be crystallised. As the chain length continues to increase the van der Waals' forces of attraction will increase, increasing the melting point. The ether quinine ionic liquids (**5c, 6c**) (Table 1 entries 5 and 6) were expected to have lower melting points than the alkyl equivalents due to the increased flexibility of the chains, discouraging regular stacking of the ions [32,33]. This is not the case for [C_1OC_2Qn][NTf_2] (**5c**) (Table 1 entry 5), which contains one ether linkage, and has a higher melting point than the C_4 alkyl analogue (**2c**) (Table 1 entry 2). The increased melting point of [C_1OC_2Qn][NTf_2] (**5c**) may be due to weak interactions formed due to the electronegative oxygen atom. The longer chain [$C_1OC_2OC_2$Qn][NTf_2] (**6c**) (Table 1, entry 6), has a lower melting point. Presumably the increased flexibility [34] due to the inclusion of two ether groups, has overcome additional interactions and prevented long range ordering [35]. This disruption of ion packing is sufficient to allow [$C_1OC_2OC_2$Qn][NTf_2] (**6c**) to form a room temperature ionic liquid. We believe this to be the first room temperature ionic liquid reported based on the quinine backbone.

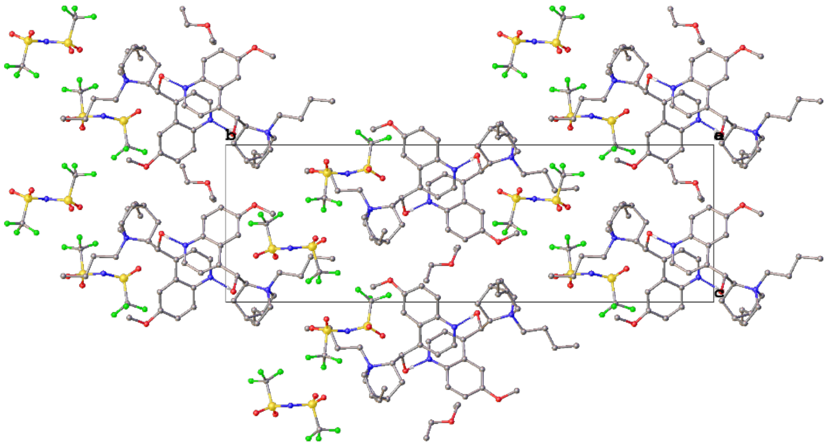


Figure 4: Packing diagram of [C_4Qn][NTf_2].

Decomposition temperature and Hammett basicity follow the same trend as melting point described above. Initially Hammett basicity increases with chain length. This may be due to disruption of the hydrogen bonding network discussed above. When the hydrogen bonding network is strong the quinoline nitrogen interacts with the hydroxyl group and is less available to deprotonate the indicator. When the hydrogen bonding network is weaker the quinoline is better able to deprotonate the indicator and the Hammett basicity increases. This is supported by the relatively high basicity of the ether quinine ionic liquids (**5c, 6c**) (Table 1 entries 5 and 6). **5c** and **6c** are expected to have flexible chains which will disrupt the ion packing to a greater degree than the alkyl quinine ionic liquids (**1c**-**4c**). This will disrupt the hydrogen bonding network freeing the quinoline nitrogen to act as a base. [C_8Qn][NTf_2] (**4c**) has a lower Hammett basicity than expected (Table 1, entry 4). As discussed for melting point, decreased ion-ion interaction caused by the disruption in hydrogen bonding is possibly reversed by increase the van der Waals' forces of attraction. This may prevent the quinoline nitrogen deprotonating the indicator molecule. Alternately, the long chain may hinder the deprotonation of the indicator molecule by preventing contact between the ionic liquid and the indicator.

Trends in thermal stability are not clear and the behaviour exhibited is complex. Increasing chain length has been reported to reduce thermal decomposition temperatures in imidazolium ionic liquids [36,37]. Basicity can also affect thermal stability, as the basicity increases there is a greater potential for self-decomposition due to the nucleophilic attack of one cation on another. Neutral quinine begins to decompose around 200 °C (ESI Figure S7) and there is an important molecular component to decomposition. Ether quinine ionic liquids **5c** and **6c** (Table 1, entries 5 and 6) have reduced decomposition temperatures compared to the alkyl quinine ionic liquids (**1c**-**4c**) of similar chain length (Table 1 entries 1-4). This is to be expected as ether functionalities are prone to cleavage and ionic liquids with ether chains tend to have lower decomposition temperatures [38]. The decomposition temperatures compare favourably with traditional basic ionic liquids [BMIM][OH] (90 °C) [39] and [BMIM][OAc] (180 °C) [40]. DABCO based ionic liquids tend to decompose at temperatures above 300 °C [41,42] but are often over-alkylated leading to a mixture of mono and di-alkylated species which are difficult to separate. The quinine ionic liquids have the advantage of being derived from renewable sources, selective alkylation of one nitrogen atom, and cleaner synthesis by using Me-THF.

It has been discussed above that the cationic nitrogen can withdraw electron density from the basic nitrogen in ionic liquids [7]. In systems based on quinoline the two nitrogen atoms are distant, and Spartan calculations [31] carried out on [MeQn][NTf_2] (**1c**) (Figure 5) suggest that the effect is small, as the electrostatic charge on the quinoline nitrogen was found to be similar before (-0.578) and after (-0.560) alkylation of the quinuclidine nitrogen, (the more negative value has greater electron density). Figure 5 displays the quinoline electron density in red. This is significant for the use of quinine ionic liquids as basic catalysts.

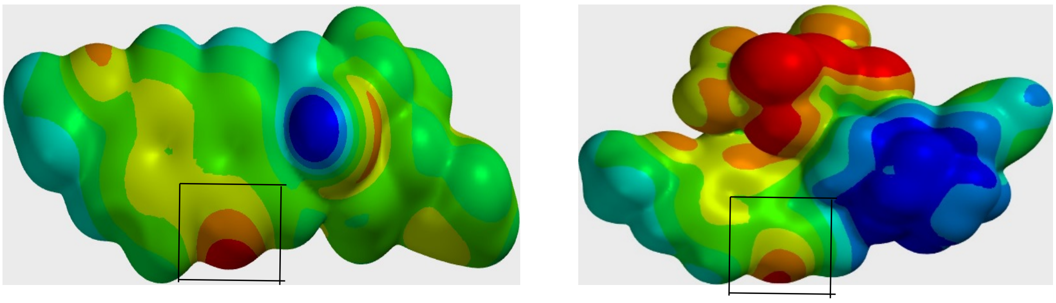


Figure 5: Electron density model of; Left) Quinine. Right) [MeQn][NTf_2]. Quinoline nitrogen is boxed in each case.

3.3. Quinine ionic liquids as basic catalysts

The Knoevenagel condensation was introduced as a test reaction for base catalysed reactions in ionic liquids by Davis and co-workers [43]. In this work the Knoevenagel is used as a demonstration of the catalytic ability of the quinine ionic liquids. The basicity of the ionic liquids was indicated by measuring their ability to act as catalysts for the Knoevenagel condensation of malononitrile and benzaldehyde (Figure 6), with yields ranging from 78-94 %. Control experiments showed that the product was not produced in the absence of a basic catalyst (Table 3, entry 1). The ether quinine ionic liquids (**5c, 6c**) exhibit higher yields than the analogous alkane chain ionic liquids (Table 3 entries 3, 5, 6, 7). This may be due to the disruption of the hydrogen bonding between the cation and quinoline, as discussed for melting point and / or due to interaction between the ether oxygens and the cation rather than the quinoline nitrogen, conserving basicity and enabling these catalysts to deprotonate the substrate more easily. The contained yield of Knoevenagel condensation (Table 3) does not follow the trend in Hammett basicity (Table 1). This could be due to a number of factors. For example steric hindrance of the longer chain ionic liquids may inhibit the catalyst access to the substrate, while the difference in van der Waals' interactions may contribute to either a reduction or increase in the interaction between the catalyst and substrate. Additionally the conditions used to measure the Hammett basicity are different to those used in the reaction. The highest contained yield was observed for $[\mathrm{C_1OC_2OC_2Qn}][\mathrm{NTf_2}]$ (**6c**), and this suggests that good liquid behaviour crossed with high Hammett basicity is a recipe for a good basic catalyst.

Recycling was tested for $[\mathrm{MeQn}][\mathrm{NTf_2}]$ (**1c**) (section 2.8.2.). A 30 minute reaction time was used to analyse recycling at yields lower than 90 %. Solvent was removed under vacuum and the product extracted into ether before filtering to recover the insoluble ionic liquid catalyst. The catalyst was dried under vacuum and reused. $[\mathrm{MeQn}][\mathrm{NTf_2}]$ (**1c**) was used for a total of four reactions with little change in activity (Figure 7). This is a facile recycling procedure compared to column chromatography used to recycle quinine from a reaction mixture [44]. The quinine ionic liquids demonstrated improved catalytic activity (Table 3 entries 2-8) and improved thermal stability compared to neutral quinine. Considering this alongside the ease of recycling, there are clear benefits to converting from quinine to quinine ionic liquids.

The quinine ionic liquids produced higher yields than traditional bases (Table 3 entries 9, 10) and quinine itself (Table 3 entry 8). This suggests that the molecular functionality of the catalyst is important and it does not act solely as a base. Theoretical calculations have shown that the elimination of hydroxide to form the final product is the rate-limiting step in a similar Knoevenagel condensation in methanol [45]. The polar nature of the ionic liquid would favour this elimination, potentially hetero-functionality in the base could assist elimination of hydroxide from the substrate. The yields obtained are comparable to literature results. Keithellakpam *et al.* [25] used a basic cation based on hexamethylenetriamine (HMTA) in water to catalyse the same reaction. The isolated yields in Keithellakpam's system ranged from 82 % to 100 %. The catalyst loading was 5-30 mole % (compared to 10 mole % ionic liquid concentration in this work). Xu *et. al.* [46] prepared a series of DABCO based ionic liquids and used 15 mole % catalyst in water, obtaining yields of 83-100 %. We have previously used a series of binary alkoxide ionic liquids, with general formula $[\mathrm{Pyrr_{14}}][\mathrm{NTf_2}]_x[\mathrm{O^iPr}]_{1-x}$, to catalyse this reaction. 1 mol % of the binary ionic liquids produced yields of 24-89 % [9]. Quinine ionic liquids are used here in a higher mole % and may be less basic than the binary ionic liquids. This could lead to the use of quinine ionic liquids to selective deprotonate a less acidic hydrogen atom on a complex molecule, leaving less reactive positions unchanged. We envisage them finding uses in other base catalysed reactions beyond the Knoevenagel condensation.

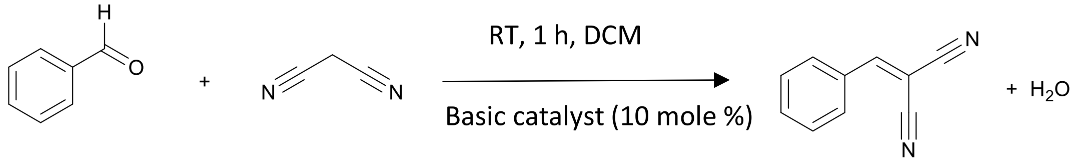


Figure 6: Knoevenagel condensation between benzaldehyde and malononitrile.

Table 3: Contained yield of Knoevenagel condensation catalysed by 10 mole % basic catalyst.

Entry	Catalyst	Hammett Basicity (H_)	Contained Yield[a] (±, SD)	Benzaldehyde Conversion (±, SD)	Malononitrile Conversion (±, SD)
1	None	NA	0	< 1	< 1
2	[MeQn][NTf$_2$] (**1c**)	8.51	79 (0.8)	95 (1.4)	86 (0.8)
3	[C$_4$Qn][NTf$_2$] (**2c**)	8.65	86 (4.9)	92 (3.7)	90 (2.1)
4	[C$_6$Qn][NTf$_2$] (**3c**)	9.40	78 (2.2)	92 (1.2)	86 (0.9)
5	[C$_8$Qn][NTf$_2$] (**4c**)	8.44	81 (1.4)	94 (2.2)	86 (0.5)
6	[C$_1$OC$_2$Qn][NTf$_2$] (**5c**)	8.72	88 (3.3)	89 (2.1)	90 (1.7)
7	[C$_1$OC$_2$OC$_2$Qn][NTf$_2$] (**6c**)	9.95	94 (4.5)	97 (2.4)	92 (5.7)
8	Quinine	9.72	63 (3.7)	99 (0)	86 (2.1)
9	DABCO	9.80	62 (2.1)	99 (0)	99 (0)
10	DBU	10.17	74 (4.1)	99 (0)	89 (6.9)

Conditions: Malononitrile (0.11 g, 1.72 mmol), benzaldehyde (0.18 g, 1.66 mmol), basic catalyst (10 mol %), DCM (0.31 g, 1:1 wt. % with reagents) (RT, stir rate 500 RPM and time 1 h). [a] Obtained from ^{1}H NMR against a known mass of ethyl trifluoroacetate, value is an average of three reactions.

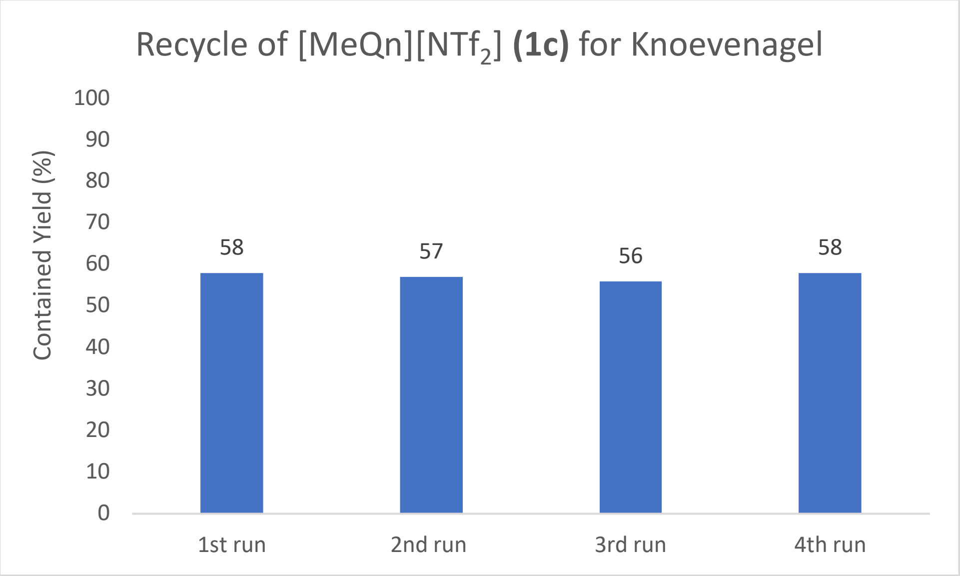


Figure 7: Contained yield in recycling experiments of Knoevenagel condensation catalysed by [MeQn][NTf$_2$] (**1c**).

[C$_6$Qn][NTf$_2$] (**3c**), [C$_1$OC$_2$Qn][NTf$_2$] (**5c**) and [C$_1$OC$_2$OC$_2$Qn][NTf$_2$] (**6c**) were found to fluoresce under UV light (see the Graphical abstract). The higher melting point ionic liquids (**1c, 2c, 4c**) fluoresced when in solution. This could potentially allow for use in fluorescence-based applications. As well as acting as basic catalysts the quinine ionic liquids have a wide range of potential uses based on their fluorescence, their antimicrobial properties [47] and their potential for enantiomeric separations [21] or enantiomeric reactions [48].

4. Conclusions

Six quinine ionic liquids have been synthesised, including one which is low melting and one room temperature ionic liquid. The ionic liquids prepared exhibit high Hammett Basicity and have been used to successfully catalyse the Knoevenagel condensation of Malononitrile and Benzaldehyde. Recycle of [MeQn][NTf$_2$] (**1c**) was possible for at least four reactions without loss of activity. These new salts may be applied to other base catalysed reactions and find additional uses due to their fluorescence and the chiral properties of quinine.

Conflicts of interest

There are no conflicts of interest to declare.

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Appendix A. Supplementary Data

Electronic supplementary information (ESI) available: Hammett basicity, Knoevenagel condensation yield calculation Spectra (NMR, FTIR, TGA, DSC), Crystallographic information, Spartan modelling.

References

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[1] N.V. Plechkova, K.R. Seddon, Applications of ionic liquids in the chemical industry, Chem. Soc. Rev. 37 (2008) 123-150. https://doi.org/10.1039/B006677J.

[2] M.J. Earle, K.R. Seddon, Ionic liquids. Green solvents for the future, Pure Appl. Chem. 72 (2000) 1391-1398. https://doi.org/10.1351/pac200072071391.

[3] R.A. Olofson, W.R. Thompson, J.S. Michelman, Heterocyclic nitrogen ylides, J. Am. Chem. Soc. 86 (1964) 1865-1866. https://doi.org/10.1021/ja01063a051.

[4] A.K.L. Yuen, A.F. Masters, T. Maschmeyer, 1,3-Disubstituted imidazolium hydroxides: Dry salts or wet carbenes?, Catal. Today. 200 (2013) 9-16. https://doi.org/10.1016/j.cattod.2012.04.007.

[5] D.R. MacFarlane, J.M. Pringle, K.M. Johansson, S.A. Forsyth, M. Forsyth, Lewis base ionic liquids, Chem. Commun. (2006) 1905-1917. https://doi.org/10.1039/B516961P.

[6] S.A. Forsyth, U. Fröhlich, P. Goodrich, H.Q.N. Gunaratne, C. Hardacre, A. McKeown, K.R. Seddon, Functionalised ionic liquids: synthesis of ionic liquids with tethered basic groups and their use in Heck and Knoevenagel reactions, New J. Chem. 34 (2010) 723–731. https://doi.org/10.1039/B9NJ00729F.

[7] U. Frölich, Chirality and ionic liquids [PhD Thesis]. Queen’s University Belfast, (2005).

[8] S.A. Ghumro, S. Saleem, M. al-Rashida, N. Iqbal, R.D. Alharthy, S. Ahmed, S.T. Moin, A. Hameed, N,N-Dimethylpyridin-4-amine (DMAP) based ionic liquids: evaluation of physical properties via molecular dynamics simulations and application as a catalyst for Fisher indole and 1H-tetrazole synthesis, RSC Adv. 7 (2017) 34197-34207. https://doi.org/10.1039/C7RA06824G.

[9] P. McNeice, A.C. Marr, P.C. Marr, M.J. Earle, K.R. Seddon, Binary Alkoxide Ionic Liquids, ACS Sus. Chem. Eng. 6 (2018) 13676-13680. https://doi.org/10.1021/acssuschemeng.8b04299.

[10] K. M. Bothwell, P.C. Marr, Taming the Base Catalyzed Sol–Gel Reaction: Basic Ionic Liquid Gels of SiO_2 and TiO_2, ACS Sus. Chem. Eng, 5 (2017) 1260-1263. https://doi.org/10.1021/acssuschemeng.6b02772.

[11] K.M. Bothwell, F. Lorenzini, P.C. Marr, A.C. Marr, Basic Ionic Liquid Gels for Catalysis: Application to the Hydrogen Borrowing Mediated Dehydration of 1,3-Propanediol, ACS. Sus. Chem. Eng. 7 (2019) 2686-2690. https://doi.org/10.1021/acssuschemeng.8b05762.

[12] P.J. Pelletier, J.B. Caventou, Recherches chimiques sur les quinquinas, Ann. Chim. et Phys. 15 (1820) 289.

[13] E.N. Jacobsen, I. Marko, W.S. Mungall, G. Schroeder, K.B. Sharpless, Asymmetric Dihydroxylation via Ligand-Accelerated Catalysis, J. Am. Chem. Soc. 110 (1988) 1968-1970. https://doi.org/10.1021/ja00214a053.

[14] K. Sharma, J.R. Wolstenhulme, P.P. Painter, D. Yeo, F. Grande-Carmona, C.P. Johnston, D.J. Tantillo, M.D. Smith, Cation-Controlled Enantioselective and Diastereoselective Synthesis of Indolines: An Autoinductive Phase-Transfer Initiated 5-endo-trig Process, J. Am. Chem. Soc. 137 (2015) 13414-13424. https://doi.org/10.1021/jacs.5b08834.

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[15] C. Richter, K.V.S. Ranganath, F. Glorius, Enantioselective α-Arylation of Cyclic Ketones Catalyzed by a Combination of an Unmodified Cinchona Alkaloid and a Palladium Complex, Adv. Synth. Catal. 354 (2012) 377-382. https://doi.org/10.1002/adsc.201100669.

[16] P. Wasserscheid, A. Bösmann, C. Bolm, Synthesis and properties of ionic liquids derived from the 'chiral pool', Chem. Commun. 3 (2002) 200-201. https://doi.org/10.1039/B109493A.

[17] G.-H. Tao, L. He, N. Sun, Y. Kou, New generation ionic liquids: cations derived from amino acids, Chem. Commun. 28 (2005) 3562-3564. https://doi.org/10.1039/B504256A.

[18] K. Fukumoto, M. Yoshizawa, H. Ohno, Room Temperature Ionic Liquids from 20 Natural Amino Acids, J. Am. Chem. Soc. 127, (2005) 2398-2399. https://doi.org/10.1021/ja043451i.

[19] V.B. Saptal, B.M. Bhanage, Bifunctional Ionic Liquids Derived from Biorenewable Sources as Sustainable Catalysts for Fixation of Carbon Dioxide, ChemSusChem. 10 (2017) 1145-1151. https://doi.org/10.1002/cssc.201601228.

[20] H. Wu, T. Liu, P. Wu, Preparation of imidazole type of ionic liquid derived from quinine alkaloid derivative, CN Pat., 105330662, 2016.

[21] T.E. Sintra, M.G. Gantman, S.P.M. Ventura, J.A.P. Coutinho, P. Wasserscheid, P.S. Schulz, Synthesis and characterization of chiral ionic liquids based on quinine, L-proline and L-valine for enantiomeric recognition, J. Mol. Liq. 283 (2019) 410-416. https://doi.org/10.1016/j.molliq.2019.03.084.

[22] M.J. Earle, presented in part at QUILL meeting, Belfast, 2004.

[23] M.P.S. Mousavi, B.E. Wilson, S. Kashefolgheta, E.L. Anderson, S. He, P. Bühlmann, A. Stein, Ionic Liquids as Electrolytes for Electrochemical Double-Layer Capacitors: Structures that Optimize Specific Energy, ACS Appl. Mater. Interfaces. 8 (2016) 3396-3406. https://doi.org/10.1021/acsami.5b11353.

[24] A. Berkessel, B. Seelig, S. Schwengberg, J. Hescheler, A. Sachinidis, Chemically Induced Cardiomyogenesis of Mouse Embryonic Stem Cells, *ChemBioChem*. 11 (2010) 208-217. https://doi.org/10.1002/cbic.200900345.

[25] S. Keithellakpam, N. Moirangthem, W.S. Laitonjam, A simple and efficient procedure for the Knoevenagel condensation catalyzed by [MeHMTA][BF4] ionic liquid *Indian J. Chem. Sect B*. 54 (2015) 1157-1161.

[26] V. Pace, P. Hoyes, L. Castoldi, P. Domínguez de Maria, A.R. Alcántara, 2-Methyltetrahydrofuran (2-MeTHF): A Biomass-Derived Solvent with Broad Application in Organic Chemistry, ChemSusChem. 5 (2012) 1369-1379. https://doi.org/10.1002/cssc.201100780.

[27] L.P. Hammett and A.J. Deyrup, A Series Of Simple Basic Indicators. I. The Acidity Functions Of Mixtures Of Sulfuric And Perchloric Acids With Water, J. Am. Chem. Soc. 54 (1932) 2721-2739. https://doi.org/10.1021/ja01346a015.

[28] C. Thomazeau, H. Olivier-Bourbigou, L. Magna, S. Luts, B. Gilbert, Determination of an Acidic Scale in Room Temperature Ionic Liquids, J. Am. Chem. Soc. 125, (2003) 5264-5265. https://doi.org/10.1021/ja0297382.

[29] W. Li, Z. Zhang, B. Han, S. Hu, J. Song, Y. Xie, X. Zhou, Switching the basicity of ionic liquids by CO2, Green Chem. 10 (2008) 1142-1145. https://doi.org/10.1039/B811624E.

[30] C. Rizzo, F. D'Anna, R. Noto, Functionalised diimidazolium salts: the anion effect on the catalytic ability, RSC Adv. 6 (2016) 58477-58484. https://doi.org/10.1039/C6RA12037G.

[31] SPARTAN PC Software using programme BLYP3 and basis 6-31G(D).

[32] E.I. Cooper, C.A. Angell, Versatile organic iodide melts and glasses with high mole fractions of LiI: Glass transition temperatures and electrical conductivities, Solid State Ionics. 9-10 (1983) 617-622. https://doi.org/10.1016/0167-2738(83)90304-1.

[33] H. Shen, Z. Chen, T. Xiao, Exploring the Relation among Free Volume, Electrostatic Interaction, and Side Chain Flexibility of Ether-Functionalized Ionic Liquids by Molecular Dynamics Simulations. ChemistrySelect, 2 (2017) 5545-5551. https://doi.org/10.1002/slct.201700912.

[34] Z.-B. Zhou, K. Tatsumi, Low-Melting, Low-Viscous, Hydrophobic Ionic Liquids: Aliphatic Quaternary Ammonium Salts with Perfluoroalkyltrifluoroborates, Chem. Eur. J. 11 (2005) 752-766. https://doi.org/10.1002/chem.200400817.

[35] A. Triolo, O. Russina, R. Carniti, H. Shirota, H.Y. Lee, C.S. Santos, N.S. Murthy, E. Castner Jr., Comparing intermediate range order for alkyl- vs. ether-substituted cations in ionic liquids, Chem. Commun. 48 (2012) 4959-4961. https://doi.org/10.1039/C2CC31550E.

[36] M. Montanino, M. Carewska, F. Alessandrini, S. Passerini, G.B. Appetecchi, The role of the cation aliphatic side chain length in piperidinium bis(trifluoromethansulfonyl)imide ionic liquids, Electrochim Acta. 57 (2011) 153-159. https://doi.org/10.1016/j.electacta.2011.03.089.

[37] N.L. Lancaster, T. Welton, G.B. Young, A study of halide nucleophilicity in ionic liquids, J. Chem. Soc., Perkin Trans. 2 (2001) 2267-2270. https://doi.org/10.1039/B107381H.

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[38] K.C. Lethesh, W. Dehaen, K. Binnemans, Base stable quaternary ammonium ionic liquids, RSC Adv. 4 (2014) 4472-4477. https://doi.org/10.1039/C3RA45126G.

[39] H. Luo, Z. Zhai, W. Fan, W. Cui, G. Nan, Z. Li, Monoacylglycerol Synthesis by Glycerolysis of Soybean Oil Using Alkaline Ionic Liquid, Ind. Eng. Chem. Res. 54 (2015) 4923-4928. https://doi.org/10.1021/ie5049548.

[40] A.J. Kunov-Kruse, P.L. Thomassen, A. Riisager, S. Mossin, R. Fehrmann, Absorption and Oxidation of Nitrogen Oxide in Ionic Liquids, Chem. Eur. J. 22 (2016) 11745-11755. https://doi.org/10.1002/chem.201601166.

[41] M. Yoshizawa-Fujita, K. Johansson, P. Newman, D.R. MacFarlane, M. Forsyth, Novel Lewis-base ionic liquids replacing typical anions, Tetrahedron Lett. 47 (2006) 2755-2758. https://doi.org/10.1016/j.tetlet.2006.02.073.

[42] C. Chiappe, B. Melai, A. Sanzone, G. Valentini, Basic ionic liquids based on monoquaternized 1,4-diazobicyclo[2.2.2]octane (dabco) and dicyanamide anion: Physicochemical and solvent properties, Pure Appl. Chem. 81 (2009) 2035-2043. https://doi.org/10.1351/PAC-CON-08-11-01.

[43] D.W. Morrison, D.C. Forbes, J.H. Davis Jr, Base-promoted reactions in ionic liquid solvents. The Knoevenagel and Robinson annulation reactions, Tetrahedron Lett. 42 (2001) 6053-6055. https://doi.org/10.1016/S0040-4039(01)01228-X.

[44] K. Jain, S. Chaudhuri, K. Pal, K. Das, The Knoevenagel condensation using quinine as an organocatalyst under solvent-free conditions, *New. J. Chem.* 43 (2019), 1299-1304. https://doi.org/10.1039/C8NJ04219E

[45] E.V. Dalessandro, H.P. Collin, M.S. Valle, J.R. Pliego Jr., Mechanism and free energy profile of base-catalyzed Knoevenagel condensation reaction, RSC Adv. 6 (2016) 57803-57810. https://doi.org/10.1039/C6RA10393F.

[46] D.-Z. Xu, Y. Liu, S. Shi, Y. Wang, A simple, efficient and green procedure for Knoevenagel condensation catalyzed by [C4dabco][BF4] ionic liquid in water, Green Chem. 12 (2010) 514-517. https://doi.org/10.1039/B918595J.

[47] M.D. Joyce, M.C. Jennings, C.N. Santiago, M.H. Fletcher, W.M. Wuest, K.P.C. Minbiole, Natural product-derived quaternary ammonium compounds with potent antimicrobial activity, J. Antibiot. 69 (2016) 344-347. https://doi.org/10.1038/ja.2015.107.

[48] A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, The Catalytic Asymmetric Knoevenagel Condensation, Angew. Chem. Int. Ed. 50 (2011) 1707-1710. https://doi.org/10.1002/anie.201006319.