Electronic Supplementary Information (ESI)

Enhanced membrane transport of pharmaceutically active protic ionic liquids

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Contents

General

The silicone membranes (thickness 0.005 inch) produced by Sterilin Ltd., UK, were used as supplied. Bromohexine hydrochloride (≥ 98) was purchased from Fluka, sodium ibuprofen (≥ 99.5 %) was supplied by Sigma and propylene glycol (≥ 99%) was purchased from Biotech Pharmaceuticals. All chemicals were used without further purification.

The synthesis and characterisation data of butylammonium acetate, heptylammonium acetate and tuammoniumheptane salicylate were reported in our previous work.[1, 2]

NMR spectra were recorded in d_6-DMSO (Cambridge Isotope Laboratories) on a Bruker Avance 400 (9.4 Tesla magnet) with a 5 mm broadband autotunable probe with Z-gradients and BACS 60 tube autosampler. Each resonance is reported according to the following convention: chemical shift (δ) measured in parts per million (ppm) from the reference signal tetramethylsilane, multiplicity, observed coupling constants (*J* Hz), number of hydrogen atoms and assignment. Multiplicities are reported as a singlet (s), doublet (d), quartet (q), or a multiplet (m).

Electrospray Mass Spectrometry (ESI) was carried out on the Micromass Platform II API QMS Electrospray Mass Spectrometer with a cone voltage of 25 V or 35 V, using methanol as the mobile phase. Analyses were conducted in both positive (ESI^+) and negative (ESI^-) modes.

Karl Fischer analysis was performed on a 831 KF Coulometer which uses the coulometric titrator system. Hydranal Coulomat AG was used as the titration solution.

An Anton Paar DMA 5000 density meter was used to measure the density of the liquids. The density meter is based on the "oscillating U-tube principle". The viscosity measurements were collected using an Anton Paar AMVn viscosity meter.

Conductivity measurements were performed on a locally designed dip cell probe containing two platinum wires sheathed in glass. The cell constant was ascertained with a solution of 0.01 M KCl at 25 ^oC. The conductivities were obtained by measuring the complex impedance spectra between 1 MHz and 0.01 Hz on a Solatron SI 1296 Dielectric interface at 5 ^oC (±1 ^oC) intervals. A Eurotherm 2204e temperature controller, interfaced to the Solatron and a cartridge heater set in a brass

block with a cavity for the cell, was used to control the temperature. A K-type thermocouple was set in the block adjacent to the cell.

Membrane studies were performed on a Digilab FTS 3000MX Excalibur series spectrometer with ATR crystal ZnSe. Good contact between the membrane and the crystal was ensured as this can influence the degree of penetration of the IR beam. An initial delay of 15 minutes was allowed for the purging of the sample chamber. Sixteen scans were taken every hour (2 cm^{-1} resolution) and an average spectrum was produced at each time point. The FTIR spectrometer was connected to a computer equipped with OPUS 6 software, which was used to analyse the spectra. In Figure 2 of the communication, all of the data, apart from salicylic acid in PG, was normalised by setting the maximum absorption of $N_TNH_3^+$ Sal^- to 100%. In the salicylic acid solution the carbonyl stretching band was monitored, which is not present in the other samples.

Synthesis and characterisation of bromohexinium ibuprofenate

A mixture of sodium ibuprofenate (3.92 g, 17.20 mmol) and bromohexinium hydrochloride (7.08 g, 17.20 mmol) in 50 ml of dry methanol was stirred overnight at room temperature. The reaction mixture was filtered through filter aid and the solution re-filtered using syringe microfilters (0.20 µm). The solvent was removed under vacuum and the yellow viscous residue was redissolved in dichloromethane. This organic phase was washed with distilled water to remove any residual sodium chloride (monitored by the silver nitrate test). The solvent was removed under vacuum leaving a clear yellow viscous liquid. The IL was further dried *in vacuo* at 55 ^{o}C for 72 hours. Yield: 84%. Glass transition temperature, Tg(DSC), 10°C/min) = -15°C (midpoint). After several months storage the sample crystallised, Tm (onset) = 28°C.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 0.84-0.86 (d, *J* 6.6, 6H, CH_3), 1.01-1.29 (m, 5H, CH), 1.33-1.34 (d, *J* 7.1, 3H, CH_3), 1.56-1.59 (m, 1H, CH), 1.74-1.85 (m, 5H, CH), 2.06 (s, 3H, CH_3), 2.34-2.40 (m, 1H, CH), 2.39-2.41 (d, *J* 7.1, 2H, CH_2), 3.55 (s, 2H, CH_2), 3.59-3.64 (q, *J* 7.1, 1H, CH), 7.08-7.10 (d, *J* 8.1, 2H, CH), 7.17-7.20 (d, *J* 8.1, 2H, CH), 7.19 (s, 1H, CH), 7.48 (s, 1H, CH).

MS (ESI): ES^+ *m/z* 377.1 (Bromohexinium$^+$, 100 %), ES- *m/z* 205.2 (Ibuprofenate$^-$, 35%), 161.2 (Ibuprofenate$^-$ – CO_2, 100%)*

* Ion is unstable in the mass spectrometer (evidenced by the identical behaviour of the sodium ibuprofenate starting material)

Water content (Karl Fischer): 407 ppm.

Cl^- content: <100 ppm

Preparation of PG solutions

The propylene glycol solutions were prepared by dissolving the compounds with stirring and heating in 1 ml of PG until saturation solution was achieved.

Table S1. Transport properties of bromohexinium ibuprofenate

Temperature (^{o}C)	**Conductivity x 10^{-7} (S cm^{-1})**	**Density (g cm^{-3})**	**Viscosity (Poise)**
25	0.034	-	-
30	0.082	-	-
35	0.176	-	-
40	0.344	-	-
45	0.641	-	-
50	1.082	-	-
55	1.721	-	-
60	2.569	-	-
65	3.681	1.264	-
70	4.956	1.260	-
75	6.445	1.255	-
80	7.986	1.250	-
85	9.544	1.246	-
90	11.112	1.242	0.533

* Density could only be measured in the range of 65-90 ^{o}C, while the viscosity could only be measured at 90 ^{o}C.

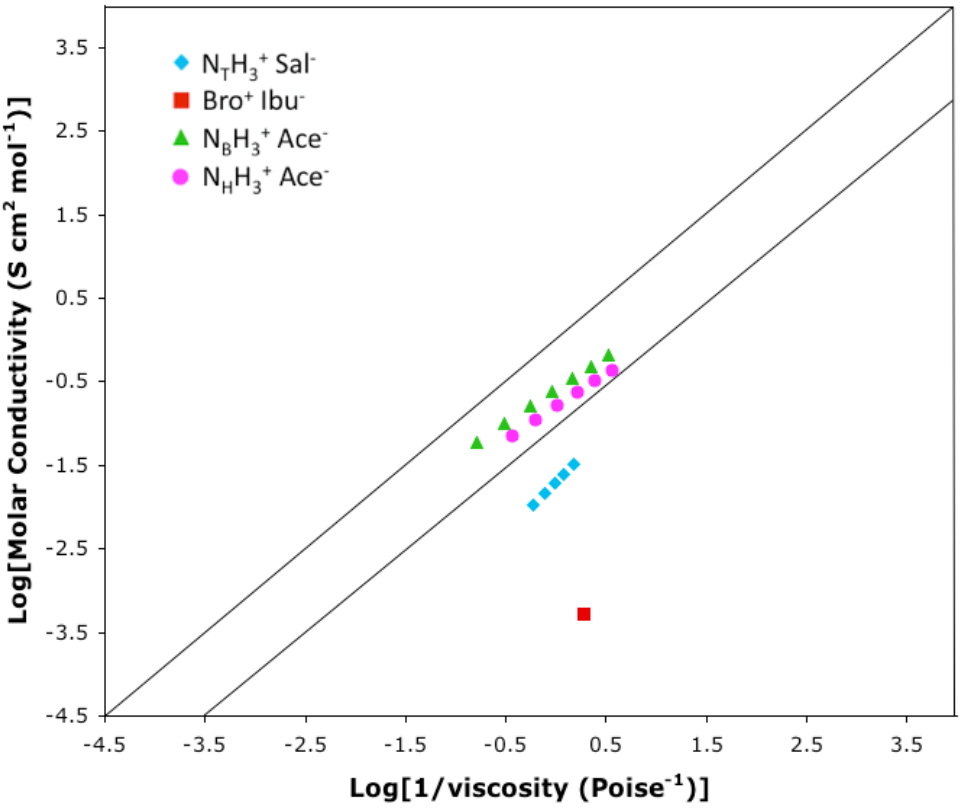

Figure S1. The Walden plot of the studied PILs ($N_TH_3^+$ Sal^-, $N_BH_3^+$ Ace^-, $N_HH_3^+$ Ace^- have been reproduced from our previous work[1, 2])

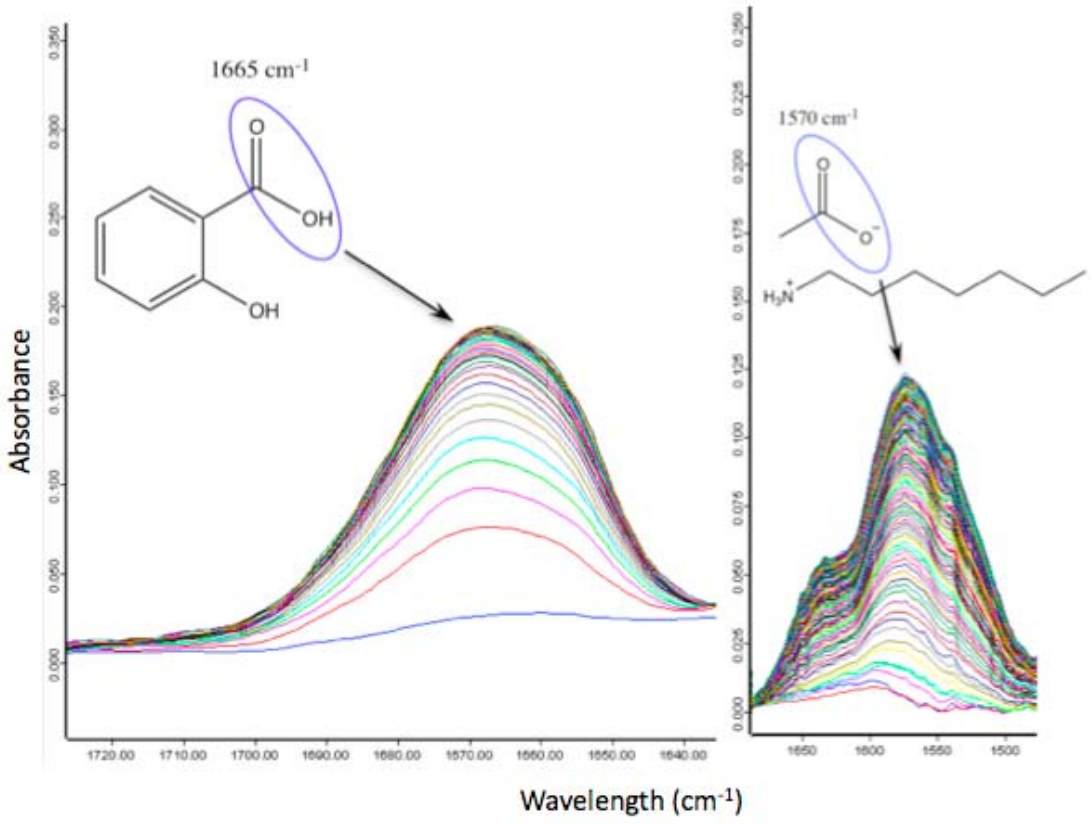

Figure S2. Examples of the FTIR experiments; membrane permeation data over time for (left) salicylic acid in PG and (right) heptylammonium acetate

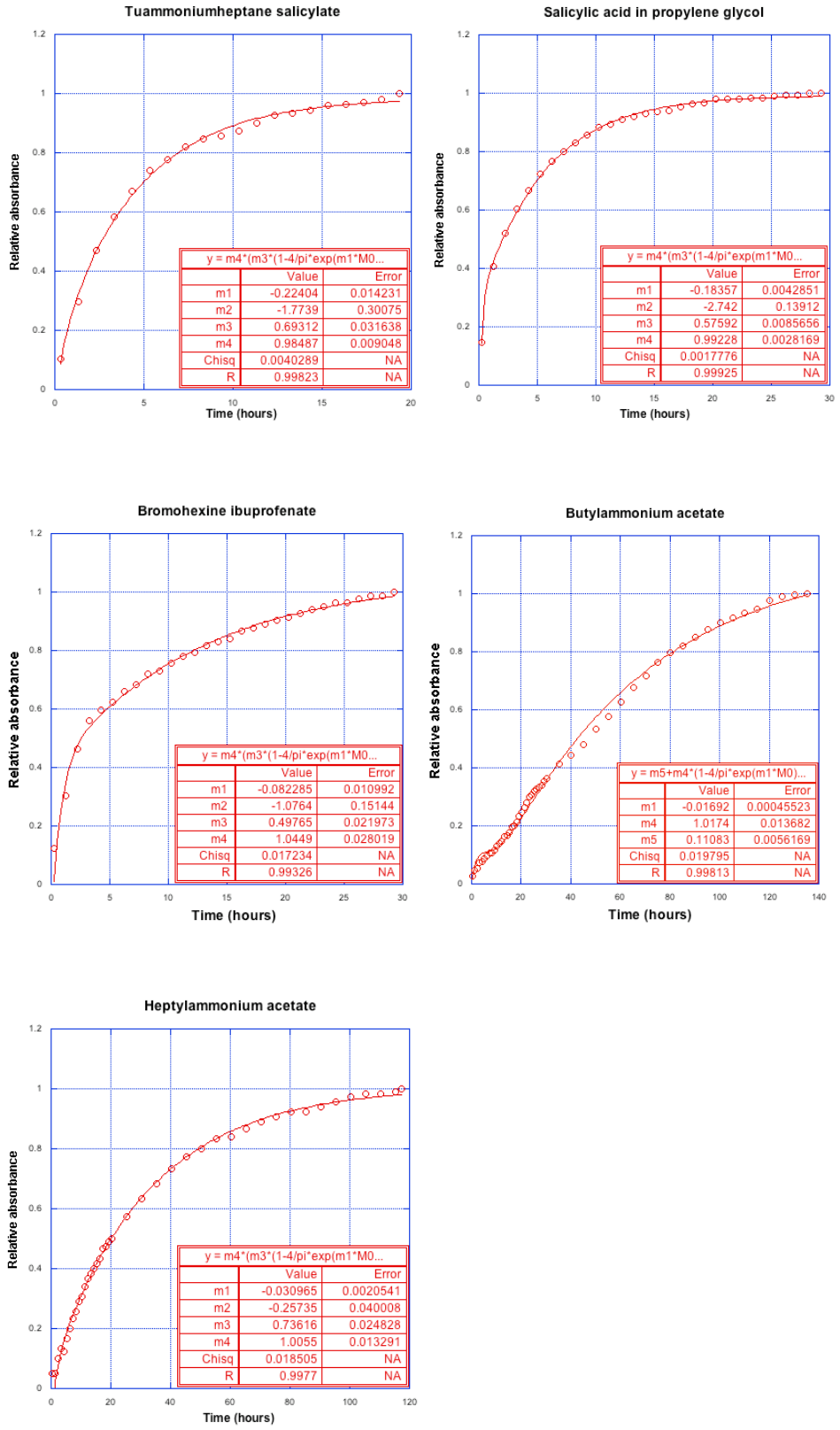

Figure S3. Diffusion profiles of the studied compounds

References

1. J. Stoimenovski, P. Dean, I. Izgorodina Ekaterina and R. MacFarlane Douglas, *Faraday Discuss.*, 2011, FD-ART-04-2011-000071.R000071.
2. J. Stoimenovski, E. I. Izgorodina and D. R. MacFarlane, *Phys. Chem. Chem. Phys.*, 2010, **12**, 10341-10347.