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Supporting Information

Confused Ionic Liquid Ions – A "Liquification" and Dosage Strategy for Pharmaceutically Active Salts

Contents

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1. General

All chemicals unless otherwise stated were purchased from Aldrich Chemical Company (Dorset, UK) and used without further purification. NMR data were recorded in d_6-DMSO at 25 °C on a Bruker (Coventry, UK) 300 DRX spectrometer and the solvent peak was used as reference. Dichlorofluoromethane-d for Vt-NMR experiments was prepared according to the literature.[1] Samples were prepared as 0.05 N solutions under nitrogen and measured with 64 scans.

Infrared spectra were recorded as neat samples from 4000-650 cm^{-1} on a Perkin-Elmer (Dublin, Ireland) Spectrum 100 FT-IR spectrometer fitted with a Universal ATR Sampling Accessory. Electrospray mass spectrometry was performed on a LCT Premier from Waters using an Advion nanomate injection system (Manchester, UK),

Water content was measured by Karl-Fischer-titration with a Mettler Toledo Titrator (Hiranuma Sangyo, Japan). The water content of all samples was found to be below 150 ppm.

Thermogravimetrical analysis was performed on a Mettler Toledo Star^e TGA/DSC unit (Leicester, UK) under nitrogen. Samples between 5 and 10 mg were placed in open alumina pans and were heated from 25 °C to 600 °C with a heating rate of 5 °C/min. Decomposition temperatures ($T_{5\%dec}$) were reported from onset to 5 wt% mass loss.

Differential scanning calorimetry (DSC) was performed on a Mettler Toledo Star^e DSC unit (Leicester, UK) under nitrogen. Samples between 5 and 10 mg were heated from 25 °C to 110 °C at a heating rate of 5 °C/min followed by a 5 min isotherm. A cooling rate of 5 °C/min to -70 °C was followed by a 5 min isotherm at -70 °C, and the cycle was repeated twice. Second and third cycles proved to be identical and only the third heating run was used for data collection.

[1] J. S. Siegel and A. L. A. Annet, *J. Org. Chem.* 1977, **53**, 2629.

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2. Experimental

*Tetrabutylphosphonium salicylate **1**.* A solution of tetrabutylphosphonium hydroxide (40% in H_2O) (3.414 g, 5 mmol) was added dropwise to a solution of salicylic acid (0.691 g, 5 mmol) in 20 mL of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 h to obtain tetrabutylphosphonium salicylate **1** in quantitative yield as colorless crystals. IR (neat) ν = 2959, 2932, 2875, 1643, 1584, 1456, 1365, 1287, 856, 809, 756, 703, 668 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.74 (dd, J_1 = 7.73 Hz, J_2 = 1.87 Hz, 1H), 7.32 (t, J_1 = 7.59 Hz, 1H), 6.77 (m, 2H), 2.20 (m, 8 H), 1.41 (m, 16 H), 0.9 (t, J = 7.06 Hz, 12 H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.1. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.9, 163.1, 131.1, 129.8, 120.6, 115.7, 115.6, 23.31 (d, J = 16.36 Hz), 22.62 (d, 4.84 Hz), 17.30 (47.27 Hz), 13.19. HRMS (ES+) [m/z] = 259.2550; (ES-) [m/z] = 137.0225. mp 57.32 °C; $T_{5\%onset}$ 307.94 °C.

Synthesis of Tetrabutylphsophonium salicylate-salicylic acid dimer. A screw-cap vial was charged with solid tetrabutylphosphonium salicylate **1** and salicylic acid under nitrogen, sealed, and carefully heated with shaking until a clear homogenous liquid was obtained. IR (neat) ν = 2964, 2937, 2874, 1654, 1598, 1485, 1459, 1253, 756, 702, 654 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.75 (dd, J_1 = 7.72 Hz, J_2 = 1.90 Hz, 2H), 7.32 (m, 2H), 6.78 (m, 4H), 2.16 (m, 8 H), 1.40 (m, 16 H), 0.9 (t, J = 7.10 Hz, 12 H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.3. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.0, 162.2, 133.8. 130.5, 117.9, 117.6, 116.8, 23.3 (d, J = 15.81 Hz), 22.63 (d, 4.22 Hz), 17.30 (47.80 Hz), 13.24. HRMS (ES+) [m/z] = 259.2549; (ES-) [m/z] = 137.0218. T_g -45.6 °C; $T_{5\%onset}$ 230.2 °C.

*Lidocainium salicylate **2**.* Lidocainium chloride monohydrate (2.881 g, 10 mmol) and sodium salicylate (1.601 g, 10 mmol) were dissolved in 50 mL of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 mL of H_2O and extracted with dichloromethane. The combined organic layers were washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Any remaining volatile material was removed under reduced pressure (0.01 mbar) to give lidocainium salicylate **2** as a colorless viscous liquid in 87% yield. IR (neat) ν = 3196, 2982, 1684, 1628, 1582, 1483, 1458, 1379, 1252, 1139, 857, 760, 664 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.05 (br s, 1H), 7.72 (dd, J_1 = 7.75 Hz, J_2 = 1.80 Hz, 1H), 7.24 (m, 1H), 7.09 (s, 3H), 6.70 (m, 2H), 3.98 (s, 2H), 3.10 (q, J = 7.28 Hz, 4 H), 2.16 (s, 6H), 1.22 (t, J = 7.34 Hz, 6 H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.9, 164.6, 161.9, 135.0, 134.0, 133.4, 130.1, 127.8, 126.9, 117.6, 116.9, 116.4, 53.3, 48.3, 18.1, 9.5. HRMS (ES+) [m/z] = 235.1814; (ES-) [m/z] = 137.0265. T_g 19.78 °C; $T_{5\%onset}$ 158.46 °C.

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3. Table S1: Physical properties of tetrabutylphosphonium salicylate-salicylic acid salts.

Entry	Compound	χ_{acid}	T_g [a] [°C]	T_m [a] [°C]	$T_{onset5\%}$ [b] [°C]	η [c,d] [mPas]	σ [e,d] [μS/cm]
1	$P(Bu)_4Sal$	0	-56.5	57.3	307.9	72.6	336.0
2	$P(Bu)_4Sal_{1.5}H_{0.5}$	0.3	-51.7	-	238.7	169.5	265.0
3	$P(Bu)_4Sal_2H$	0.5	-45.6	-	230.2	187.0	209.0
4	$P(Bu)_4Sal_{2.5}H_{1.5}$	0.6	-45.0	-	224.4	187.4	159.7
5	$P(Bu)_4Sal_3H_2$	0.75	-43.3	-	212.5	189.6	155.3
6	Salicylic acid	1	-	158.1	162.0	-	-

[a]Determined on a Mettler Toledo Star[e] DSC by heating to 110 °C at 5 °C/min and cooling at 5 °C/min to -80 °C for 3 cycles. [b]Determined on a Mettler Toledo Star[e] TGA/DSC by heating from 25 °C to 600 °C at 5 °C/min under nitrogen. [c]Measured on a Brookfield CAP Viscometer at 50 °C. [d]Water content of all samples < 150 ppm according to Karl-Fisher titration. [c]Measured on a Mettler Toledo Conductivity meter S30 at 50 °C.

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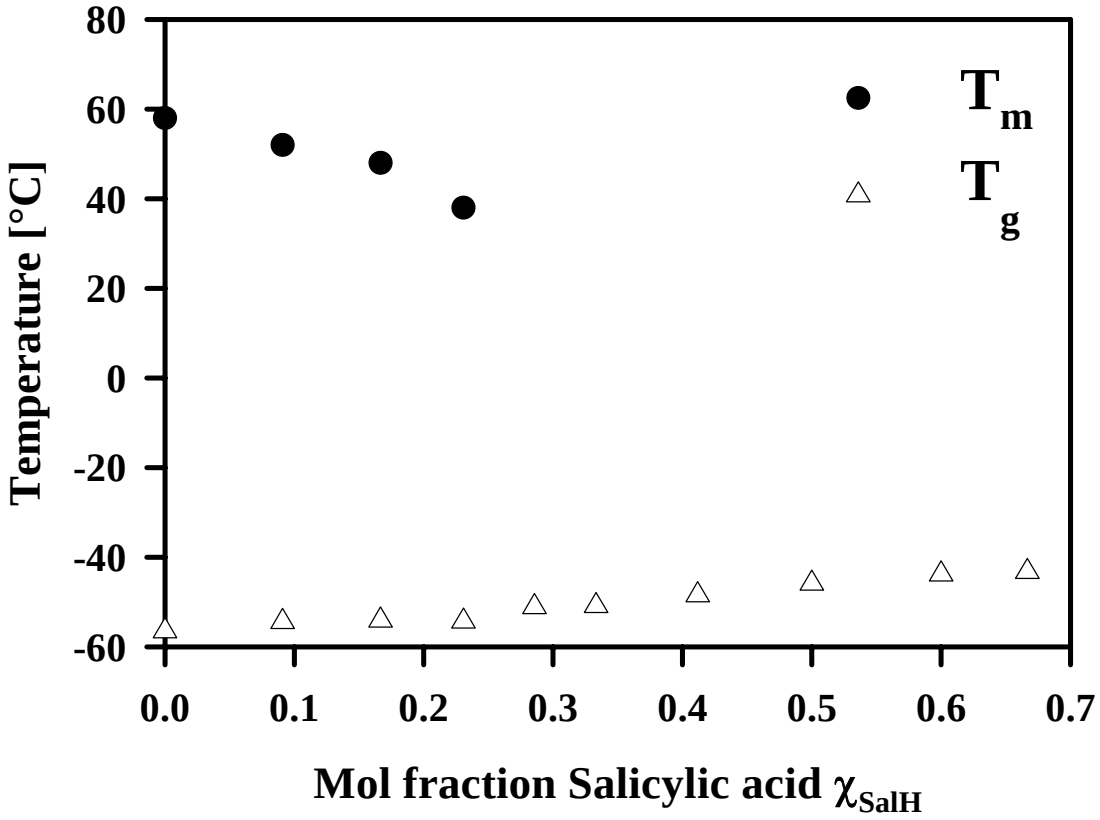
4. Figure S1: Liquifaction of solid PBu_4Sal [1] with excess salicylic acid.



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5. Figure S2: TGA traces of tetrabutylphosphonium salicylate-salicylic acid salts.