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Physical Chemistry of Ionic Liquids

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Physical chemistry of ionic liquids
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In search of pure liquid salt forms of aspirin: ionic liquid approaches with acetylsalicylic acid and salicylic acid†

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We present an ionic liquid (IL) approach towards a dual functional liquid salt form of aspirin using different pharmaceutically active cations composed of antibacterials, analgesics, local anesthetics, and antiarrhythmic drugs in combination with acetylsalicylic acid or its metabolite salicylic acid and discuss stability of these ILs in comparison to solid salts. Several low-melting or liquid salts of salicylic acid with dual functionality and promising properties were isolated and characterized; however, although such ILs with aspirin could be prepared, they suffer from limited stability and slowly decompose into the corresponding salicylate ILs when exposed to moisture.

Introduction

With an estimated world-wide consumption of 40 000 metric tons per year, aspirin (acetylsalicylic acid) which was discovered in 1853, is still one of the most prominent and widely used medicines with an incredible spectrum of properties.[1] Apart from its exceptional analgesic, anti-pyretic, and anti-inflammatory properties, it is commonly used in the primary and secondary prevention of cardiovascular diseases.[2]

Aspirin is typically administered *via* the oral route, but unfortunately possesses a number of undesired side effects in long-term use that are mainly related to its acidity and low bioavailability. Aspirin is only sparingly soluble in water (0.33 g in 100 mL) or in the acidic environment of the stomach, resulting in undissolved particles adhering to the gastro-intestinal mucosea and causing topical irritation and gastric distress.[3] Once absorbed in the small intestine, acetylsalicylic acid is rapidly metabolized to its main metabolite salicylic acid, thereby irreversibly acetylating and inhibiting COX-1 oxygenase.[4] Like aspirin, salicylic acid itself is also part of the non-steroidal anti-inflammatory drug (NSAID) family and is frequently found in a wide range of medical and cosmetic formulations such as skin-care products or sunscreens.[5] Apart from problems related to the poor solubility of aspirin, the bitter taste of acetylsalicylic acid is another major drawback, with the required dosage of aspirin leading to tablets that are notoriously hard to swallow.

Considering these problems, it is readily apparent that a liquid salt formulation of aspirin could not only improve and control solubility of aspirin, but could also lead to new delivery forms and applications that might circumvent gastro-intestinal irritation. A low melting (T_m = 49.5 °C), though not liquid salt form of aspirin's main metabolite salicylic acid is already known (choline salicylate) and marketed under the brand name Bonjela® for use against mouth ulcer and for the relief of pain in teething children.[6,7]

Within the last several years, ionic liquids (ILs, salts melting below 100 °C) have evolved from their application as solvents in synthesis and catalysis[8] towards new materials (*e.g.*, energetic liquids[9] or lubricants[10]) and recently have even entered the field of pharmaceuticals.[11–13] In our previous work on pharmaceutically active ILs, we demonstrated that IL forms of active pharmaceutical ingredients (APIs) can provide new and unique properties compared to the solid pharmaceutical forms, with the possibility of improved performance such as controlled solubility and drug delivery. A liquid salt form also eliminates the possibility of polymorphism and thus polymorphic conversion which can dramatically alter a drug's solubility and thus dosages.

Apart from the advantages of the liquid state, a second biologically active counterion can be included which might lead to dual functional analgesics.[12] However, it should be noted that the dual functionality inherent in ILs is rarely exploited, and while the active ions could be pharmacologically independent, they might also act in a synergistic or antagonistic manner with one active ion counteracting the side effects of the active ingredient. The judicious selection of appropriate active cations in combination with acetylsalicylate or salicylate as anion might therefore not only allow new liquid formulations of aspirin or salicylic acid with modified physical properties and improved solubility, but could also introduce new therapeutic properties not inherent to the pure neutral form, thus expanding the range of application.

In this study, we have paired salicylate (a) and acetylsalicylate (b) with a set of cations (Fig. 1) of variable biological activity covering antimicrobial or antibacterial activity (tetrabutylphosphonium **1**, cetylpyridinium **2**, benzethonium **3**, benzalkonium **4**, hexetidinium **5**), analgesics (tramadolium **6**),

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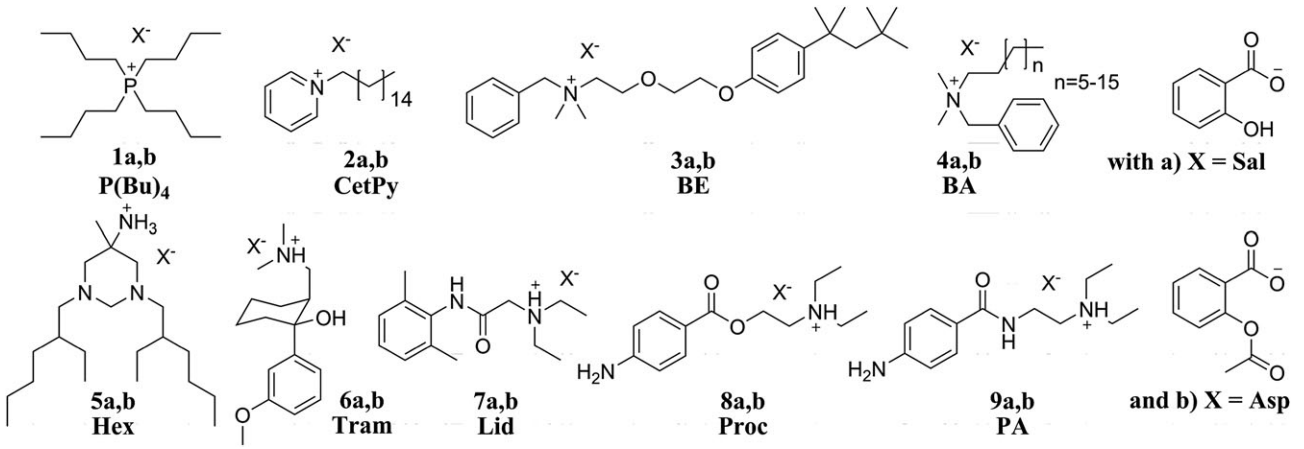

Fig. 1 Antibacterial (**1**, **2**, **3**, **4**, **5**), analgesic (**6**), local anesthetic (**7**, **8**) and antiarrhythmic (**9**) cations used in combination with the salicylate (**a**) and acetylsalicylate anion (**b**).

local anesthetics (lidocainium **7**, procainium **8**), and an antiarrhythmic (procainiumamide **9**). The antimicrobial properties of quaternary phosphonium salts such as tetrabutylphosphonium in ILs have been previously described.[14,15] Cetylpyridinium chloride, benzethonium chloride and benzalkonium chloride are all typical examples of long-chain quaternary ammonium cations with antibacterial properties against Gram-positive and Gram-negative bacterial strains.[16] Interactions of their chloride salts with salicylic acid have been previously studied, and indeed can be frequently found in preservatives or skin-care products.[17] Similarly, hexetidine is a well known antibacterial and antifungal agent often used in mouthwashes.[18]

In comparison to the permanent quaternary ammonium compounds, the local anesthetic or antiarrhythmic cations of the caine family (lidocaine, procaine, and procainamide), as well as the atypical opioid analgesic tramadol, are protonated in ionized form, thus giving rise to protic ILs. The advances of co-administration of the atypical opioid tramadol with aspirin in patient-controlled analgesia (PCA) in the management of post-surgical pain have been previously discussed; however a combination of tramadol with injectable lysine acetylsalicylate was used.[19] Additionally, synergistic antinociceptive interaction effects between aspirin and tramadol were studied in rats, clearly indicating an interaction between these drugs.[20]

Results and discussion

Synthesis and characterization

Salicylate salts (Table 1). Since most of the selected active cation candidates are readily available as the corresponding hydrochloride salts, the synthesis of the salicylate ILs can be achieved by a straightforward metathesis reaction with the alkali salt of the acid under aqueous conditions. The new salts can then be extracted with dichloromethane and, after extractive removal of inorganic impurities with H_2O, isolated by evaporation in good yields. As an exception, tetrabutylphosphonium salicylate **1a** was prepared by reaction of the commercially available tetrabutylphosphonium hydroxide solution (40% in H_2O) with salicylic acid.

In terms of an efficient, waste-free synthesis it should be noted that protic salicylate ILs can be alternatively prepared in a solvent-free reaction from the free base and salicylic acid. For example, lidocainium salicylate **7a** and procainium salicylate **8a** were also prepared by melting a stoichiometric mixture of base and salicylic acid at ~100 °C to obtain a clear, free flowing liquid. The spectroscopic and thermal properties of these ILs (**7a** and **8a**) prepared by simple melting were found to be identical to the materials obtained *via* conventional anion metathesis.

Similarly, hexetidinium salicylate **5a** was directly synthesized by reaction of hexetidine with salicylic acid, since only the free base was commercially available. This solvent-free preparation is clearly advantageous compared to conventional metathesis, since solvents and stoichiometric NaCl waste are prevented. Furthermore, the ILs are obtained in high purity without halide, metal, or solvent impurities, as is necessary for pharmaceutical applications.

Table 1 Yields and thermochemical properties of salicylate and acetylsalicylate ILs

Compound	Yield[a]	T_g[b]	T_m[b]	$T_{5\%onset}$[c]
$P(Bu)_4$Sal **1a**	>99	−56.47	57.32	307.94
CetPySal **2a**	56	—	73.97	205.61
BESal **3a**	87	−13.72	—	167.76
BASal **4a**	92	51.01	96.02	171.95
HexSal **5a**	>99	—	106.81	182.14
TramSal **6a**	89	—	176.17(dec)[c]	177.16
LidSal **7a**	87	19.78	—	158.46
ProcSal **8a**	99	13.87	—	187.33
PASal **9a**	74	19.87	—	159.21
CetPyAsp **2b**	33	—	61.31	115.14
BEAsp **3b**	82	2.84	—	154.22
TramAsp **6b**	83	13.78	—	169.64
LidAsp **7b**	76	−13.97	—	120.71

[a] Isolated yield. [b] Glass transitions (T_g) and melting points (T_m) determined on a Mettler Toledo Star^e DSC by heating to 110 °C at 5 °C min^{-1} and cooling at 5 °C min^{-1} to −70 °C for 3 cycles. [c] Onset to 5% decomposition temperature ($T_{5\%onset}$) determined on a Mettler Toledo Star^e TGA/DSC by heating from 25 °C to 600 °C at 5 °C min^{-1} under nitrogen.

Acetylsalicylate salts (Table 1). The preparation of acetylsalicylate ILs is complicated by the low stability of aspirin and its alkali salts in water, and only a few salts could be isolated in pure form. The spontaneous hydrolysis of aspirin to salicylic acid and acetic acid in various media and even in contact with moisture has been the subject of numerous publications, and a half-life of 153.3 ± 3.7 h has been determined for aspirin in unbuffered H_2O at 25 °C.[21] Hence it was necessary to avoid isolation of the sodium salt of acetylsalicylic acid and to perform salt formation and metathesis in a one-step procedure by addition of one equivalent base to a suspension of acetylsalicylic acid and the cation in its hydrochloride form in H_2O.

Bases such as NaOH, K_2CO_3, and even $NaOAc{\cdot}3H_2O$ led to complete or partial decomposition of the acetylsalicylate anion; however, a change to a weaker base and lower temperature was successful. Optimum conditions were found with $NaHCO_3$ at 0 °C in combination with short reaction times of 10 min which allowed the isolation of some of the acetylsalicylate ILs without decomposition.

Thermal properties. With the exception of tramadolium and hexetidinium salts **5a** and **6a**, all obtained salicylates were found to be low melting solids or liquids at room temperature fitting the definition of ILs (Table 1). It is interesting to note that cetylpyridinium salicylate **2a**, benzalkonium salicylate **3a**, and hexetidinium salicylate **5a** display a second endothermic transition before the melting point at 60.63 °C, 71.39 °C, and 100.03 °C, respectively.

Comparison of the glass transition temperatures or melting points for the acetylsalicylate salts to the corresponding salicylates reveals in general a significant reduction of glass transition temperatures or melting points for the acetylsalicylates. Except for cetylpyridinium acetylsalicylate **2b**, that readily crystallizes into a low melting (61.31 °C) colorless solid, all of the acetylsalicylates were obtained as viscous liquids with only a glass transition observable. This significant reduction of melting point compared to the corresponding salicylates is likely to be caused by the absence of inter- or intramolecular hydrogen bonds in the acetylsalicylate anion.

It is a common assumption that liquid formulations of pharmaceuticals suffer from limited stability. However, we have previously shown in the pharmaceutically active IL lidocainium docusate, that pharmaceutically active ionic liquids do not necessarily exhibit limited stability, but can even lead to improved thermal stability of a parent solid active compound.[12] In this study, we found examples of both higher thermal stability (for some salicylates) and lower stability (for the acetylsalicylates) in their IL forms *vs.* the parent neutral or salt forms.

In general, single-step decompositions with good thermal stabilities ≥ 160 °C were obtained for all salicylate salts, with even a doubled thermal stability of tetrabutylphosphonium salicylate **1a** ($T_{5\%onset}$ 307.94 °C) compared to pure salicylic acid ($T_{5\%onset}$ 162.01 °C). More importantly, the thermal stabilities of the protic ILs are higher than the corresponding free bases of the cations, and sometimes even higher than the hydrochloride form. For example, the observed onset temperature for the viscous liquid lidocainium salicylate **7a** of 158.46 °C is higher than that of solid lidocaine ($T_{5\%onset}$ 147.04 °C). This clearly demonstrates that the liquid or glass-like state *per se* is not necessarily related to a reduced thermal stability.

By contrast, the thermal stability of acetylsalicylate ILs is reduced compared to the salicylate, but still in an acceptable range >100 °C. It is interesting to note that single-step decompositions were obtained in thermogravimetric analysis (TGA) without a preliminary liberation of acetic acid.

On the other hand, the long-term stability of a pharmaceutically active IL—as of any salt—is directly related to the stability of the ions. Successful formation of a stable IL requires a stable ion, as can be easily demonstrated using aspirin as example, whose anions are well known to rapidly hydrolyze.[22] Thus, even though ILs based on aspirin could be isolated without decomposition and with sufficient thermal stability, they suffer from limited long-term stability. For example, we found that lidocainium acetylsalicylate **7b**, when stored at room temperature and under air, slowly degraded to the corresponding salicylate. The degradation could be monitored by integration of aromatic signals in proton NMR and based on this data, 33% hydrolysis of **7b** to lidocainium salicylate **7a** was observed within one week (Fig. 2).

The intramolecular hydrolysis resulting in the decomposition of the molecule into salicylic and acetic acid could be theoretically prevented under strictly anhydrous conditions. However, this will require difficult handling and expensive production such as the use of moisture-proof packaging or the coating with a buffering layer for each individual dose.[23] This

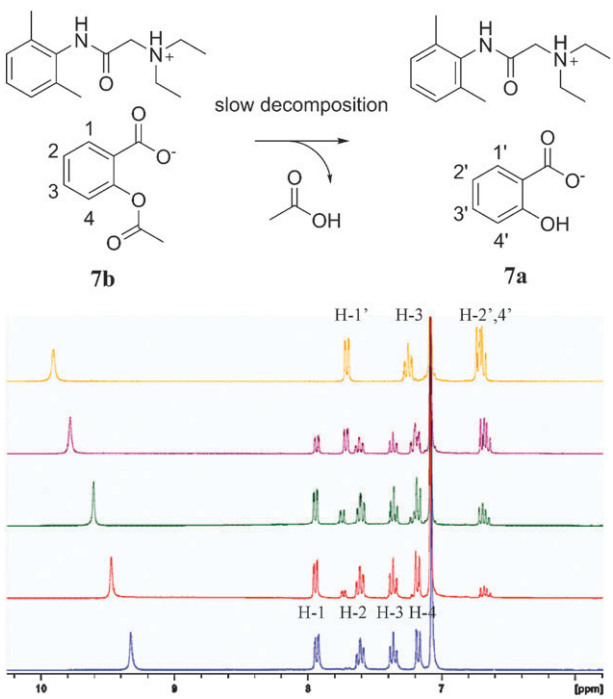

Fig. 2 The aromatic region of the ^{1}H NMR spectra of lidocainium acetylsalicylate **7b** immediately after isolation (blue), after 1 d (red), after 2 d (green), and after 1 week (purple) and of pure lidocainium salicylate **7a** (yellow).

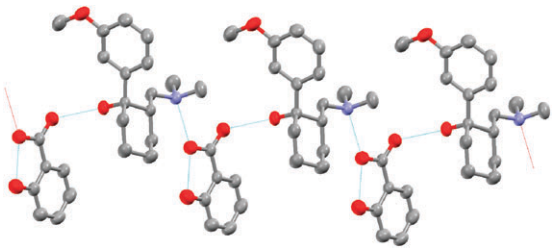

Fig. 3 Hydrogen bonded chain of cations and anions in **6a**. The hydrogen atoms have been removed for clarity.

might argue for a design based on the stable salicylate anion, which is the main metabolite of acetylsalicylate anyway.

Crystal structure. Single crystals of the high-melting salt tramadolium salicylate, **6a**, could be grown by slow evaporation of ethanol and the composition and structure of this salt was confirmed by single crystal X-ray analysis (Fig. 3). The structure is dominated by the hydrogen bonding between the cation and anion. The hydroxyl group of the anion donates an intramolecular hydrogen bond to the carboxylate group. The same oxygen atom that accepts this hydrogen bond also accepts a hydrogen bond from the protonated nitrogen atom of the cation. The cation's hydroxyl group donates a third hydrogen bond to the other oxygen atom in the carboxylate group, but from a neighboring anion. The result is a linear hydrogen bonded chain of tramadolium and acetlyacetonate which propagates along the unit cell direction *b*. The hydrogen bonded chains pack in such a manner that the aromatic portions of both cation and anion form an aromatic rich region; with edge to edge stacking interactions at *ca.* 3.7 Å between the methoxyphenyl rings of the cations.

Conclusions

We have successfully prepared IL forms of aspirin and salicylic acid in combination with different pharmaceutically active cations. Although there are stability issues with aspirinate ILs, promising dual functional ILs based on salicylate could be prepared and characterized. Given the growing interest in antimicrobial properties of ILs, we particularly envision the use of dual functional salicylate ILs with antibacterial cations for antimicrobial and biocide application.[24] However, it appears that the limited stability of acetylsalicylate ILs may prevent their therapeutic application unless moisture can be rigorously excluded. Although an IL strategy should be considered as another tool in drug development, design, and delivery, such an approach may not be applicable in every instance.

Experimental

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.

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 dried ILs was found to be below 1000 ppm.

Thermogravimetric analysis was performed on a Mettler Toledo Star^e TGA/DSC (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^{-1}. 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 (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^{-1} followed by a 5 min isotherm. A cooling rate of 5 °C min^{-1} 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. Transitions above ambient temperature were confirmed optically on a Stuart SMP3 melting point apparatus.

Synthesis

Tetrabutylphosphonium salicylate 1a. 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 **1a** 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, 4H), 1.41 (m, 8H), 0.9 (t, J = 7.06 Hz, 6H). ^{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, J = 4.84 Hz), 17.30 (d, J = 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.

General procedure for the synthesis of salicylate ILs as exemplified by cetylpyridinium salicylate, 2a. Cetylpyridinium chloride monohydrate (20.64 g, 56 mmol) and sodium salicylate (8.96 g, 56 mmol) were dissolved in 100 mL of acetone/H_2O 1 : 1 and stirred overnight at room temperature. The remaining suspension was diluted with 100 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

cetylpyridinium salicylate **2a** in 56% yield as a colorless waxy solid. IR (neat) ν = 3229, 2917, 2850, 1627, 1578, 1484, 1457, 1386, 1334, 1106, 761 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 9.12 (d, J = 6.08 Hz, 2H), 8.59 (t, J = 8.29 Hz, 1H), 8.16 (t, J = 7.27 Hz, 2H), 7.64 (d, 7.54 Hz, 1H), 7.12 (t, J = 7.54, 1H), 6.57 (m, 2H), 4.59 (t, J = 7.44 Hz, 2H), 1.88 (m, 2H), 1.22 (s, 27H), 0.84 (t, J = 7.14 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 171.8, 163.4, 145.8, 145.2, 131.4, 130.2, 128.4, 121.1, 116.1, 160.0, 61.2, 31.7, 31.2, 29.4, 29.3, 29.2, 29.1, 28.8, 25.8, 22.5, 14.2. HRMS (ES+) [m/z] = 304.3004; (ES−) [m/z] = 137.0228. Mp 73.97 °C; $T_{5\%onset}$ 205.61 °C.

Benzethonium salicylate 3a. Prepared following the procedure used to make **2a**, **3a** was obtained as a colorless glass in 87% yield. IR (neat) ν = 3402, 2958, 1633, 1589, 1484, 1454, 1383, 1243, 1131, 857, 760, 705 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 7.65 (m, 1H), 7.53 (m, 5H), 7.26 (d, J = 8.9 Hz, 2H), 7.10 (s, 1H), 6.82 (d, J = 8.9 Hz, 2H), 6.57 (m, 2H), 4.61 (s, 2H), 4.11 (s, 2H), 4.00 (m, 2H), 3.82 (s, 2H), 3.39 (m, 2H), 3.02 (s, 6H), 1.67 (s, 2H), 1.28 (s, 6H), 0.66 (s, 9H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 171.3, 163.1, 156.0, 141.5, 133.1, 131.3, 130.2, 129.9, 128.8, 128.1, 126.9, 120.5, 115.8, 113.6, 68.9, 67.4, 66.6, 63.9, 62.6, 56.3, 49.7, 37.5, 32.0, 31.5. HRMS (ES+) [m/z] = 412.3205; (ES−) [m/z] = 137.0226. T_g −13.72 °C; $T_{5\%onset}$ 167.76 °C.

Benzalkonium salicylate 4a. Prepared following the procedure used to make **2a**, **4a** was obtained as a colorless solid in 92% yield. IR (neat) ν = 3404, 2921, 2854, 1630, 1585, 1454, 1379, 859, 759, 704 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 7.66 (dd, J_1 = 7.61 Hz, J_2 = 1.77 Hz, 1H), 7.52 (m, 5H), 7.10 (t, J = 7.30 Hz, 1H), 6.58 (m, 2H), 4.55 (s, 2H), 3.25 (m, 2H), 2.96 (s, 6H), 1.77 (m, 2H), 1.25 (m, 20H), 0.86 (t, J = 6.89 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 171.2, 163.1, 132.9, 131.1, 130.2, 129.9, 128.9, 128.2, 120.8, 115.7, 115.6, 66.2, 63.5, 49.1, 31.3, 29.0, 28.9, 28.7, 28.5, 25.8, 22.1, 21.8, 13.9. HRMS (ES-) [m/z] = 137.0244. Mp 96.02 °C; $T_{5\%onset}$ 171.95 °C.

Hexetidinium salicylate 5a. A solution of hexetidine (3.39 g, 10 mmol) and salicylic acid (1.69 g, 10 mmol) in 20 mL of acetone was stirred for 2 h at room temperature. The solvent was evaporated, and the remaining solid was dried at 0.1 mbar for 24 h to obtain hexetidine salicylate **5a** as a colorless solid in quantitative yield. IR (neat) ν = 2924, 1639, 1483, 1458, 1379, 1340, 1254, 857, 760, 665 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 8.01 (br s, 3H), 7.69 (dd, J_1 = 7.75 Hz, J_2 = .18 Hz, 1H), 7.15 (t, J = 7.92 Hz, 1H), 6.63 (m, 2H), 3.47 (m, 1H), 2.78 (m, 2H), 2.07 (m, 6H), 1.25 (m, 21 H), 0.84 (m, 12H), ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 171.9, 162.6, 131.5, 130.0, 120.2, 116.1, 115.8, 76.0, 60.2, 59.8, 58.1, 50.9, 35.8, 35.5, 30.7, 30.5, 28.3, 28.2, 23.9, 23.8, 22.6, 22.5, 20.2, 14.0, 13.99, 10.6, 10.4. HRMS (ES+) [m/z] = 340.3685; (ES−) [m/z] = 137.0239. Mp 106.81 °C; $T_{5\%onset}$ 182.14 °C.

Tramadolium salicylate 6a. Tramadolium hydrochloride (1.499 g, 5 mmol) and sodium salicylate (0.801 g, 5 mmol) were dissolved in 50 mL of acetone/H_2O 1 : 1 and stirred overnight at room temperature. Acetone was evaporated and the precipitating solid was collected *via* filtration, washed with H_2O and dried under reduced pressure (0.01 mbar) to isolate **6a** as a colorless solid in 89% yield. IR (neat) ν = 3295, 2946, 1579, 1459, 1328, 1250, 1176, 1044, 857, 764 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 7.69 (dd, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.19 (m, 1H), 7.08 (m, 2H), 6.79 (m, 1H), 6.66 (m, 2H), 3.76 (s, 3H), 3.56 (br s, 1H), 2.83 (t, J = 11.9 Hz, 1H), 2.52 (s, 6H), 2.33 (d, J = 13.0 Hz, 1H), 2.24 (m, 1H), 1.89 (m, 1H), 1.64 (m, 7H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 172.0, 162.3, 159.2, 150.0, 131.9, 120.1, 129.1, 119.5, 117.2, 116.5, 117.2, 116.5, 115.9, 111.5, 111.1, 73.9, 59.4, 55.0, 43.0, 40.5, 40.4, 25.7, 24.6, 21.2. HRMS (ES+) [m/z] = 264.1972; (ES−) [m/z] = 137.0226. Mp 176.17 °C; $T_{5\%onset}$ 194.52 °C.

Lidocainium salicylate 7a. Prepared following the procedure used to make **2a**, **7a** was obtained 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, 4H), 2.16 (s, 6H), 1.22 (t, J = 7.34 Hz, 6H). ^{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.

Procainium salicylate 8a. Prepared following the procedure used to make **2a**, **8a** was obtained as a colorless viscous liquid in 98% yield. IR (neat) ν = 3357, 3223, 1702, 1627, 1596, 1454, 1265, 1170, 1107, 857, 765 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 7.74 (dd, J_1 = 7.58 Hz, J_2 = 1.62 Hz, 1H), 7.70 (d, J = 8.53 Hz, 2H), 7.23 (m, 1H), 6.72 (m, 2H), 6.58 (d, J = 8.76 Hz, 2H), 4.51 (t, J = 5.19 Hz, 2H), 3.44 (t, J = 5.15 Hz, 2H), 3.18 (q, J = 7.19 Hz, 4H), 1.23 (t, J = 7.27 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 172.8, 165.5, 162.0, 153.8, 132.2, 131.4, 130.2, 118.9, 117.0, 116.0, 115.1, 112.7, 58.7, 49.5, 46.8, 8.8. HRMS (ES+) [m/z] = 237.1615; (ES−) [m/z] = 137.0242. T_g 13.87 °C; $T_{5\%onset}$ 187.33 °C.

Procainamidium salicylate 9a. Prepared following the procedure used to make **2a**, **9a** was obtained as a colorless viscous liquid in 74% yield. IR (neat) ν = 3348, 3229, 1624, 1598, 1568, 1484, 1454, 1380, 1291, 1190, 762, 664 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 8.44 (t, J = 5.6 Hz, 1H), 7.72 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.23 (m, 1H), 6.71 (m, 2H), 6.54 (d, J = 8.6 Hz, 2H), 3.60 (s, 2H), 3.19 (m, 6H), 1.23 (t, J = 7.1 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 172.5, 166.9, 162.2, 152.0, 132.2, 130.2, 128.8, 120.4, 119.1, 116.8, 116.0 112.5, 50.0, 46.7, 34.3, 8.6. HRMS (ES+) [m/z] = 236.1746; (ES−) [m/z] = 137.0223. T_g 19.87 °C; $T_{5\%onset}$ 159.21 °C.

General procedure for the synthesis of acetylsalicylate ILs exemplified by lidocainium acetylsalicylate, 7b. Lidocaine hydrochloride monohydrate (2.89 g, 10 mmol) and acetylsalicylic acid (1.80 g, 10 mmol) were dissolved in 30 mL of

acetone/H_2O 1 : 1 and chilled to 0 °C. Sodium hydrogen carbonate (0.84 g, 10 mmol) was dissolved in 2 mL H_2O and added dropwise. The clear solution was stirred 15 min at 0 °C until gas evolution ceased, diluted with 50 mL H_2O, and extracted with dichloromethane. The combined organic layers were washed successively with H_2O 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 at a temperature below 40 °C. Any remaining volatile materials were removed under high vacuum to yield lidocainium acetylsalicylate **7b** as a colorless viscous liquid in 83% yield. IR (neat) ν = 3184, 2976, 1756, 1684, 1368, 1191, 1088, 916, 751 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 9.32 (br s, 1H), 7.93 (dd, J_1 = 7.73 Hz, J_2 = 1.62 Hz, 1H), 7.61 (t, J = 7.75 Hz, 1H), 7.36 (t, J = 7.76 Hz, 1H), 7.17 (d, J = 8.05 Hz, 1H), 7.07 (s, 3H), 3.27 (s, 2H), 2.70 (q, J = 7.20 Hz, 4H), 2.25 (s, 3H), 2.15 (s, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 169.9, 168.7, 165.9, 150.2, 135.1, 135.0, 134.4, 131.4, 127.7, 126.4, 125.9, 124.8, 123.7, 56.2, 48.1, 20.9, 18.2, 11.7. HRMS (ES+) [m/z] = 235.1822; (ES−) [m/z] = 179.0344. T_g −13.97 °C; $T_{5\%onset}$ 120.71 °C.

Cetylpyridinium acetylsalicylate 2b. Prepared following the procedure used to make **7b**, **2b** was obtained as a colorless solid in 33% yield. IR (neat) ν = 3378, 2917, 2856, 1748, 1601, 1369, 1220, 1195, 689 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 9.12 (d, J = 5.90 Hz, 1H), 8.60 (t, J = 7.67 Hz, 1H), 8.16 (t, J = 6.97 Hz, 2H), 7.82 (dd, J_1 = 7.72 Hz, J_2 = 1.70 Hz, 1H), 7.41 (t, J = 7.37 Hz, 1H), 7.22 (t, J = 4.43 Hz, 1H), 7.01 (d, J = 7.89 Hz, 1H), 4.59 (t, J = 7.37 Hz, 2H), 2.19 (s, 3H), 1.89 (m, 2H), 1.23 (m, 27H), 0.85 (t, J = 7.09 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 171.5, 163.0, 144.8, 131.1, 129.9, 128.0, 124.9, 122.7, 120.6, 115.7, 60.7, 31.3, 30.8, 29.1, 29.0, 28.8, 28.7, 28.4, 25.4, 22.1, 21.8, 21.2, 13.9. HRMS (ES+) [m/z] = 304.3011; (ES−) [m/z] = 179.0344. Mp 61.31 °C; $T_{5\%onset}$ 115.14 °C.

Benzethonium acetylsalicylate 3b. Prepared following the procedure used to make **7b**, **3b** was obtained as a colorless glass in 82% yield. IR (neat) ν = 3389, 2955, 1750, 1607, 1511, 1358, 1220, 1188, 829, 709 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 7.80 (d, J = 8.06 Hz, 1H), 7.60 (m, 2H), 7.52 (m, 2H), 7.27 (m, 3H), 7.16 (t, J = 7.53 Hz, 1H), 6.94 (d, J = 8.10 Hz, 1H), 6.84 (d, J = 8.81 Hz, 2H), 4.68 (s, 2H), 4.12 (m, 2H), 4.01 (m, 2H), 3.84 (m, 2H), 3.59 (m, 2H), 3.05 (s, 6H), 2.17 (s, 3H), 1.69 (s, 2H), 1.30 (s, 6H), 0.69 (s, 9H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 169.3, 156.0, 149.6, 141.5, 133.2, 131.2, 130.2, 129.1, 128.8, 128.2, 126.9, 124.8, 122.5, 113.6, 68.8, 67.3, 66.6, 63.9, 62.5, 56.3, 48.7, 37.6, 32.0, 31.6, 21.3. HRMS (ES+) [m/z] = 412.3216; (ES−) [m/z] = 179.0335. T_g 2.84 °C; $T_{5\%onset}$ 154.22 °C.

Tramadolium acetylsalicylate 6b. Prepared following the procedure used to make **7b**, **6b** was obtained as a colorless viscous liquid in 83% yield. IR (neat) ν = 3325, 2939, 1753, 1598, 1361, 1192, 1041, 754, 702 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm) = 7.89 (dd, J_1 = 7.82 Hz, J_2 = 1.76 Hz, 1H), 7.55 (d, J = 7.84 Hz, 1H), 7.32 (t, J = 7.69 Hz, 1H), 7.22 (t, J = 7.80 Hz, 1H), 7.13 (d, J = 8.11 Hz, 1H), 7.02 (m, 2H), 6.74 (d, J = 8.43 Hz, 1H), 3.74 (s, 3H), 2.36 (m, 1H), 2.22 (s, 3H), 2.11 (s, 6H). 1.95–1.40 (m, 9H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ (ppm) = 172.4, 169.5, 167.6, 159.2, 150.7, 150.0, 131.6, 131.4, 129.1, 125.6, 123.3, 117.4, 111.4, 111.3, 74.4, 59.8, 55.0, 43.9, 41.5, 40.8, 26.7, 25.1, 21.6, 21.2. HRMS[25] (ES+) [m/z] = 264.1972; T_g. 13.78 °C; $T_{5\%onset}$ 169.64 °C.

X-Ray diffraction

Crystals of tramadolium salicylate **6a** were obtained by slow evaporation from ethanol. Data for **6a** was collected on a Siemens P4 with graphite-monochromated Mo Kα radiation at room temperature using XSCANS software and the structure was solved using direct methods and refined with SHELXTL v5. The structure was refined by full-matrix least-squares on F^2. Hydrogen atoms were added at idealised positions and a riding model (U_{ij} = 1.2U_{eq}) was used in subsequent refinement cycles. CCDC 762135.†

Crystal data for Tramadolium salicylate 6a. $C_{25}H_{33}NO_6$; Mr = 443.53 g mol^{-1}, triclinic, space group $P\bar{1}$; T = 293 K; a = 9.051(1), b = 9.834(3), c = 12.766(4) Å, α = 74.69(2), β = 89.45(2), γ = 76.56(2)°; Z = 2; V = 1064.2(5) $Å^3$; D_c = 1.253 g cm^{-3}, R_{int} = 0.0315. A total of 4990 reflections were measured for the angle range 3 < 2θ < 50° and 2576 independent reflections were used in the refinement. The final parameters were wR_2 = 0.1647; R_1 = 0.0504 [$I > 2\sigma I$].

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