

Electronic Supplementary Information

The Third Evolution of Ionic Liquids: Active Pharmaceutical Ingredients

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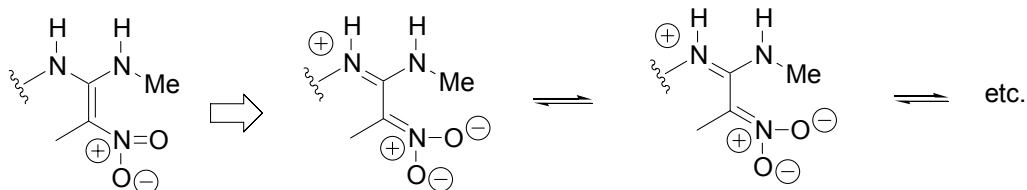
Lidocaine Docusate. In a 100 mL round-bottomed flask charged with a magnetic stirbar, 1.552 g (3.49 mmol) of sodium dioctylsulfosuccinate (sodium docusate; Aldrich, St. Louis, MO) was dissolved/suspended in 25 mL of reagent grade acetonitrile. To the stirred mixture was added, in one portion, 0.945 g (3.49 mmol) lidocaine hydrochloride (Sigma-Aldrich, St. Louis, MO). The suspension was stirred overnight, after which time the solvent was removed in vacuo. The white residue was extracted with 2 x 25 mL portions of dichloromethane, which were combined and flash filtered through small plugs of Celite and silica. The colorless solution was evaporated to leave 1.88 g (2.86 mmol, 82%) of the desired lidocaine docusate salt as a clear, colorless syrup. The product tested negative for the presence of chloride anions with silver nitrate. Differential scanning calorimetry (DSC) was used to determine melting point but only the following transitions were present: glass transition $T_g = -29$ °C and liquid-liquid transition $T_{l-l} = 78$ °C. Thermal stability data determined by thermogravimetric analysis (TGA): $T_{\text{onset}5\%} = 222$ °C, T_{onset}

= 262 °C and $T_{dec} = 287$ °C. ^1H NMR 500MHz (DMSO- d_6): 0.86 (12H, m), 1.25 (22H, m), 1.48 (2H, m), 2.17 (6H, s), 2.88 (1H, dd), 2.93 (1H, d), 3.22 (4H, m), 3.63 (1H, dd), 3.88 (4H, m), 4.17 (2H, s), 7.10 (3H, m); ^{13}C NMR 500MHz (DMSO- d_6): 8.7, 10.6, 10.7, 13.8, 17.9, 19.0, 22.3, 22.8, 22.9, 23.0, 23.1, 24.2, 24.5, 28.2, 29.4, 29.5, 29.6, 34.0, 38.0, 48.3, 59.9, 61.3, 65.9, 73.6, 126.5, 126.9, 127.8, 133.5, 134.8, 168.2, 170.9.

Solubility of LD in water was experimentally determined at room temperature (22 ± 2 °C). An amount of LD, exceeding the solubility limit, was added to deionized water (with a resistivity of 17.4 M Ω ·cm) in 20 mL glass vials. The mixture was thoroughly shaken overnight, resulting in a stably cloudy solution. Phase separation could not be reached either by letting the solution stand for several days or by centrifuging. Therefore, drops of water were gradually added until miscibility were reached. After each drop addition, the mixture was shaken again, allowing for the system to equilibrate. When the solution turned completely miscible, an aliquot was taken with a pipette, and it was diluted with fresh water for subsequent analysis by UV spectroscopy.

A series of diluted solutions of LD in water were prepared by weight with a Denver Instrument M-220D analytical balance, precise to within $\pm 1 \times 10^{-4}$ g. Their absorbance was measured at a wavelength of 192 nm with a Cary 3C UV-Vis spectrophotometer, by Varian Instruments providing a calibration line relating absorbance and concentration. The absorbance of the diluted aliquot of the saturated solution was measured, and its concentration calculated. Since the solutions were largely diluted, it was assumed that molal and molar concentrations were related by the density of the solvent, i.e. water. The solubility test was run in triplicate, and the results were found to be in reasonable agreement, within the expectable uncertainty of the method.

Ranitidine Docusate. In a 50 mL round-bottomed flask charged with a magnetic stirbar, 1.917 g (4.31 mmol) of sodium dioctylsulfosuccinate (sodium docusate; Aldrich, St. Louis, MO) was dissolved/suspended in 20 mL of reagent grade acetonitrile. To the stirred mixture was added, in one portion, 1.513 g (4.31 mmol) ranitidine hydrochloride (Sigma-Aldrich, St. Louis, MO). The deep yellow-brown suspension was stirred overnight, after which time it was filtered to remove precipitated NaCl. The solvent was removed under vacuum and the deep red-brown residue extracted with dichloromethane, the resulting solution then being flash chromatographed on silica, eluting with dichloromethane. Removal of the dichloromethane yielded the product (1.621 g, 3.83 mmol, 89%) as a deep, red-brown syrup. Differential scanning calorimetry (DSC) was used to determine the following transitions: glass transition $T_g = -12\text{ }^\circ\text{C}$ and liquid-liquid transition $T_{l-l} = 29\text{ }^\circ\text{C}$. Thermal stability data determined by thermogravimetric analysis (TGA): $T_{5\% \text{onset}} = 163\text{ }^\circ\text{C}$, $T_{\text{onset}} = 249\text{ }^\circ\text{C}$ and $T_{\text{dec}} = 278\text{ }^\circ\text{C}$. $^1\text{H-NMR}$ 300 MHz, ($\text{DMSO-}d_6$), ppm: 2.08 (overlapping m, docusate CH_3s); 1.22-1.60 (overlapping m, docusate CH, CH_2s); 2.12 (s, ranitidine $\text{N}(\text{CH}_3)_2$); 2.6 – 3.0 (overlapping m, docusate and ranitidine CH_2s); 3.35 (s, ranitidine CH_2); 3.4 – 3.6 (m, docusate CH, CH_2); 3.86 (m, overlapping docusate, ranitidine CH_2s); 4.34 (s, ranitidine CH_2); 6.4-6.2 (overlapping m, ranitidine furyl Hs, vinylic H); 7.7-7.3 and 9.7-10.0 (br singlets, ranitidine vinyl H). Both the chloride and docusate salts of ranitidine apparently exist as multiple isomers in solution potentially due to amide-like isomerism associated with the vinylic nitroamidate group. The integrated intensity of the single vinylic H is consequently spread over the possible isomeric forms (below):



Didecyldimethylammonium Ibuprofen. Didecyldimethylammonium bromide (0.001 mol) (Sigma-Aldrich, St. Louis, MO) was dissolved in 60 mL of distilled water by gentle heating and stirring. Sodium ibuprofen (0.001 mol) (Sigma-Aldrich, St. Louis, MO) was dissolved in 60 mL of distilled water by gentle heating and stirring. The two solutions were combined and the reaction mixture was heated and stirred for 30 min. Afterwards, the reaction mixture was cooled to room temperature, 60 mL of chloroform was added and the mixture was stirred for an additional 30 min. The two phases were separated and the chloroform phase was washed several times with cool distilled water to remove any inorganic salt. The presence of chloride anions was monitored by silver nitrate test. The solvent was removed on a rotary evaporator and the product, didecyldimethylammonium ibuprofen, was obtained with 91 % yield. Melting point (DSC) was not detected and glass transition $T_g = -73$ °C. Thermal stability data determined by thermogravimetric analysis (TGA): $T_{5\%onset} = 147$ °C, $T_{onset} = 168$ °C, and $T_{dec} = 194$ °C. ^1H NMR 500MHz (DMSO- d_6): 0.85 (m, 12H), 1.19 (d, 3H), 1.25 (m, 28H), 1.58 (m, 4H), 1.77 (sept, 1H), 2.35 (d, 2H), 3.00 (s, 6H), 3.22 (m, 4H), 3.86 (s, 1H), 6.92 (d, 2H), 7.14 (d, 2H); ^{13}C NMR 500MHz (DMSO- d_6): 13.8, 19.9, 21.5, 22.0, 22.1, 25.6, 28.3, 28.5, 28.7, 28.8, 29.6, 31.2, 44.2, 49.7, 49.8, 50.2, 62.6, 127.0, 127.9, 137.3.

Mouse Antinociception Tests. The effects of different doses of topical LD or LHCl dissolved in DMSO on the latency response for tail withdrawal in intact mice from a 49 °C water bath were determined. Tail withdrawal latencies were measured in seconds over a two hour interval. The data points represent the mean \pm s.e.m. before BL (base line) and 15-120 min after a 60 s tail exposure to either 10 or 100 mM LD or LHCl solutions. Asterisks reflect statistically-

significant group differences ($p \leq 0.05$, Fisher's LSD method). A baseline measurement was taken at the 0 time point and the drug was administered topically 10 min later. Figure 2a shows the administration of 1 mM LD or LHCl, resulting in a no-effect dose. Administration of a 100 mM concentration LD (Figure 2b) resulted in greater antinociceptive activity over time than LHCl as indicated by ANOVA ($F_{(4,92)} = 2.889$, $p < 0.05$), with a statistically-significant interaction between time and drug at 100 mM ($F_{(4,92)} = 17.189$, $p < 0.05$). A Fischer's LSD post-hoc analysis indicated an enhancement of activity for 100 mM LD at 5 min post drug ($p < 0.05$). There were no group differences following exposure to the lower, 1 mM concentration of LD and LHCl, establishing a no-effect dose. TW = latency response for tail withdrawal; i.e., latency is proportionate to analgesia.

Effects of topical LD and LHCl on the 47 °C warm-water tail-flick latency response of mice bearing a thermal wound place toward the tip of the tail about 1cm in length. The injury model was used to evaluate the effect of LD and LHCl under hyperalgesic conditions. The drugs were tested at 100 mM in 90% DMSO:10% H₂O. LD produced a greater antinociceptive effect over time than LHCl as indicated by a statistically-significant main effect of drug ($F_{(1,47)} = 6.515$, $p < 0.05$), time ($F_{(8,376)} = 7.377$, $p < 0.05$) and drug x time interaction ($F_{(8,376)} = 2.317$, $p < 0.05$). From a Fischer's LSD post-hoc analysis, tail withdrawal latencies produced with LD were longer than latencies produced with LHCl at 60, 90, 150, and 180 min post injury ($p < 0.05$). (BL = baseline, PI-BL = post injury baseline). BL was established and immediately afterwards the tail wound was administered. The PI-BL was established 20 min following the injury and drugs were administered immediately afterwards. TW latency was repeatedly measured in each mouse 15, 30, 60, 90, 120, 150, and 180 min later. Twelve to 16 mice were used per drug group for 12 to 16 measurements at each data point.

Suppression of PC12 Neuritic Outgrowth. PC12 cells were grown in complete medium in 1 cm diameter wells for 3 days either with no treatment (0), with NGF (50 $\mu\text{g}/\text{mL}$) alone, 4000 or 400 μM LHCl, or 400 μM LD. Cells were killed at 4000 μM with either compound. There are a total of 6 counts per bar/well. Cells were stained with nuclear red and counted using phase-contrast microscopy. Data represent the mean \pm s.e.m. of one observation per well over six wells. About an 80-100 cell cluster selected mid-center of the well-floor was examined per data point. Process with lengths equivalent to 3-4X diameter of cell body were counted as neurites.