Letters to the Editor

Biologically active protic (2-hydroxyethyl)ammonium ionic liquids. Liquid aspirin

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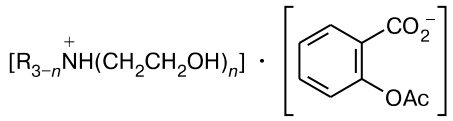
In recent years, avalanche-like growth of publications takes place in the field of chemistry and application of ionic liquids (ILs), which is the most important part of green chemistry[1—15]. However, biological properties of ILs are still to be investigated[16]. Protonated *N*-(2-hydroxyethyl)-containing amines, which comprise cations of biogenic amines and anions of bioactive organic acids, are promising biologically and pharmacologically active compounds. A typical example of this type of ILs is the recently described *N*-(2-hydroxyethyl)ammoniumformate $[HOCH_2CH_2NH_3^+]\cdot[HCOO^-]$ with a freezing point of −82 °C. However, it was recommended only as a solvent for inorganic salts and polymers[17].

In the present work, reactions of tris(2-hydroxyethyl)-, bis(2-hydroxyethyl)-, *N*,*N*-bis(2-hydroxyethyl)- *N*-methyl-, and *N*-(2-hydroxyethyl)-*N*,*N*-dimethylamines with *O*-acetylsalicylic acid (ASA, aspirin) were investigated, and novel ionic liquids **1**—**4** were obtained, which are liquid water-soluble derivatives of aspirin, suitable for intravenous injection and exhibiting anti-inflammation activity.

Salts **1**—**4** were synthesized as viscous colorless or pale yellow liquids in up to 99% yields from *N*-(2-hydroxyethyl)amines and ASA taken in equimolar ratio at 50—70 °C in methanol. In contrast to aspirin, salts **1**—**4** are water- and physiological saline-soluble, non-toxic (intra-peritoneal LD_{50} of compounds **1**—**4** for albino mice 2000 mg kg^{-1} in comparison to LD_{50} of ASA 1430 mg kg^{-1}).



1—4

n = 3 (**1**); R = H, *n* = 2 (**2**); R = Me, *n* = 2 (**3**); R = Me, *n* = 1 (**4**)

In hemocoagulation studies compounds **1** and **4** were found to show highest activity. Being injected in blood plasma in concentration $5\cdot10^{-3}$ g mL^{-1} they strongly inhibited fibrin clot formation. Anti-inflammation activity of salts **1** and **4** was studied on the rabbit model of rheumatoid arthritis with the intra-articular injection of the antigen. Solutions of **1** and **4** (1.5 mL, 10% in saline, 3 injections) were injected into the affected knee joints. This resulted in fever reduction, and ESR and protein fractions returned to normal values. Primary histological examination showed dramatic reduction of inflammation. It should be noted that activity of compound **1** was higher than that of **4**.

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IR-spectra were recorded on a Varian 3100FT-IR75 spectrophotometer. NMR spectra (CD_3OD) were recorded on a DPX-400 spectrometer (^1H, 400.13 MHz; ^{13}C, 101.62 MHz; ^{15}N, 40.53 MHz) with hexamethyldisiloxane (HMDS) as an internal standard. Alkanolamines were purified by triple distillation, and ASA — by double recrystallization from hot water.

Tris(2-hydroxyethyl)ammonium salicylate (1). Solution of 1.49 g (0.01 mol) of triethanolamine in 10 mL of methanol was added dropwise to the solution of 1.8 g (0.01 mol) of ASA in 10 mL of methanol, and the mixture was stirred for 1 h under reflux. Then the solvent was removed under vacuum. The residue was washed with ether and dried under vacuum over P_2O_5. Yield 3.28 g (99%), colorless transparent oil. ^1H NMR, δ: 7.28—6.77 (m, 4 H, C_6H_4); 5.28 (br.s, 3 H, OH); 3.85 (t, 6 H, OCH_2); 3.33 (t, 6 H, NCH_2); 2.00 (s, 3 H, CH_3COO). ^{13}C NMR, δ: 175.14 (COOH); 172.29 ($CH_3\underline{C}OO$); 162.76—117.44 (C_6H_4); 59.09 (OCH_2); 56.95 (NCH_2), 19.90 ($\underline{C}H_3COO$). ^{15}N NMR, δ: −338.8 (referenced to CH_3NO_3). IR, ν/cm^{-1}: 1626, 1590 (C=O), 2400—2550 (N^+H); 3353 (OH). Found (%): C, 54.99; H, 7.33; N, 4.37. $C_{15}H_{23}O_7N$. Calculated (%): C, 54.70; H, 7.03; N, 4.25.

Bis(2-hydroxyethyl)ammonium salicylate (2) was obtained from ASA and diethanolamine using the same procedure as for compound **1**. Yield 96%, colorless transparent oil. ^1H NMR, δ: 7.42—6.77 (m, 4 H, C_6H_4); 5.35 (br.s, 2 H, OH); 3.80 (t, 4 H, OCH_2); 3.30 (t, 4 H, NCH_2); 1.99 (s, 3 H, CH_3COO). ^{13}C NMR, δ: 177.01 (COOH); 165.02 ($CH_3\underline{C}OO$); 160.76—118.81 (C_6H_4); 58.98 (OCH_2); 57.01 (NCH_2), 20.20 ($\underline{C}H_3COO$). ^{15}N NMR, δ: −339.9. IR, ν/cm^{-1}: 1625, 1588 (C=O); 2400—2550 (N^+H); 3390 (OH). Found (%): C, 55.08; H, 7.00; N, 4.88. $C_{13}H_{19}O_6N$. Calculated (%): C, 54.73; H, 6.71; N, 4.90.

***N,N*-Bis(2-hydroxyethyl)-*N*-methylammonium salicylate (3)** was obtained from ASA and *N*-methyldiethanolamine using the same procedure as for compound **1**, yield 91%, oil. ^1H NMR, δ: 7.32—6.70 (m, 4 H, C_6H_4); 5.31 (br.s, 2 H, OH); 3.88 (t, 4 H, OCH_2); 3.29 (t, 4 H, NCH_2); 2.92 (s, 3 H, NMe); 2.03 (s, 3 H, CH_3COO). ^{13}C NMR, δ: 175.92 (COOH); 162.47 ($CH_3\underline{C}OO$); 134.03—117.18 (C_6H_4); 58.87 (OCH_2); 56.54 (NCH_2), 20.80 ($\underline{C}H_3COO$). ^{15}N NMR, δ: −341.2. IR, ν/cm^{-1}: 1627, 1590 (C=O); 2400—2521 (N^+H); 3391 (OH). Found (%): C, 56.48; H, 7.00; N, 4.90. $C_{14}H_{21}O_6N$. Calculated (%): C, 56.17; H, 7.07; N, 4.68.

***N*-(2-Hydroxyethyl)-*N,N*-dimethylammonium salicylate (4)** was obtained from ASA and *N*,*N*-dimethylethanolamine using the same procedure as for compound **1**, yield 90%, oil. ^1H NMR, δ: 7.85—6.80 (m, 4 H, C_6H_4); 5.30 (br.s, 1 H, OH); 3.84 (t, 2 H, OCH_2); 3.32 (t, 2 H, NCH_2); 2.88 (s, 6 H, NCH_3); 2.01 (s, 3 H, CH_3COO). ^{13}C NMR, δ: 175.94 (COOH); 162.49 ($CH_3\underline{C}OO$); 134.04—117.18 (C_6H_4); 60.20 (OCH_2); 56.52 (NCH_2), 21.00 ($\underline{C}H_3COO$). ^{15}N NMR, δ: −346.1. IR, ν/cm^{-1}: 1628, 1591 (C=O); 2400—2520 (N^+H); 3378 (OH). Found (%): C, 58.28; H, 6.82; N, 5.14. $C_{13}H_{19}O_5N$. Calculated (%): C, 57.98; H, 7.11; N, 5.20.

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