Articles

Solubility of Two Stable Iminium Salts in 12 Polar Solvents

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Despite their biological importance, little is known about the physicochemical properties of iminium salts due to their high reactivity with water. Our group has synthesized several iminium salts that are unusually stable to hydrolysis. In the present work, solubility data are reported as a function of temperature for two of these compounds, namely, 8-acetamide-2,4,4,8-tetramethyl-3-azabicyclo[3.3.1]non-2-ene perchlorate and 8-benzamide-2-phenyl-4,4,8-trimethyl-3-azabicyclo[3.3.1]non-2-ene perchlorate, in 12 different polar solvents. Thermodynamic quantities related to the solution process are calculated.

Introduction

Many workers have devoted efforts to study the chemistry of iminium salts because of the important role they play in a number of biological processes.[1,2] However, little is known regarding the physicochemical and clinical or pharmaceutical properties of these compounds, since the iminium group (R−NH$^+$=R′) is readily hydrolyzed under normal atmospheric conditions and is consequently unmanageable for practical applications.

By the mid-1980s our group found that reactions of limonene with nitriles in the presence of perchloric acid yield, through a Ritter mechanism, bicyclic iminium perchlorates which do not undergo hydrolysis even when dissolved in acid or neutral solutions.[3−5] Furthermore, X-ray measurements performed on single crystals showed that these salts might possess interesting dielectric properties[6,7] while preliminary tests performed on tissue samples and on mice indicate that these compounds have a significant depressive action on the cardiac muscle.

Consequently, it was decided to begin a systematic study of the properties of these compounds and their solutions. In this paper we report the solubility values of 8-acetamide-2,4,4,8-tetramethyl-3-azabicyclo[3.3.1]non-2-ene perchlorate (ATABNEP) and 8-benzamide-2-phenyl-4,4,8-trimethyl-3-azabicyclo[3.3.1]non-2-ene perchlorate (BETABNEP) in the solvents listed in Table 1 as a function of temperature.

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Table 1. Solvents Used in This Work[a]

solvent	dielectric constant	density g·mL^{-1}	source
water	78.3	0.997	bidistilled
methanol	32.7	0.787	Merck 99.6%
ethanol	24.6	0.785	Merck 99.8%
1-propanol	20.3	0.799	Merck 99.7%
2-propanol	19.4	0.781	Merck 99.7%
1-butanol	17.5	0.810	Mallinckrodt 99.6%
1,2-propanediol	32.0	1.036	Aldrich >99%
2-ethoxyethanol	13.4	0.930	Aldrich >99%
propanone	20.7	0.785	Fluka >99%
ethanonitrile	36.0	0.777	Aldrich >99%
propanonitrile	29.7	0.772	Fluka >99%
propenonitrile	33.0	0.806	Carlo Erba >99%

[a] Densities correspond to data given at 25 °C.

Experimental Section

ATABNEP was prepared as previously described,[3] employing 2.80 g of (+)-limonene (Merck) in 120 mL of acetonitrile (Aldrich) containing 3.80 mL of concentrated perchloric acid (Merck). The obtained solid was recrystallized several times from absolute ethanol, yielding 2.0 g of the pure salt, as confirmed by IR, NMR, and mass spectroscopy.

BETABNEP was synthesized by dissolving 14.0 g of (+)-limonene (Merck) in 600 mL of benzonitrile (Aldrich) containing 3.80 mL of concentrated perchloric acid (Merck). The resulting solid was also recrystallized from absolute ethanol, and finally, 8.83 g of pure BETABNEP was obtained. The salt was characterized through its IR, NMR, and mass spectra.

Solubility measurements were carried out by the following method: (a) Flasks containing saturated solutions of each salt−solvent pair were thermostated and shaken

10.1021/je010263o CCC: $22.00
Published on Web 10/17/2002

Table 2. Solubility Values in Molar Fraction Units X_s for ATABNEP in Each Solvent

	$X_s \times 10^3$				
solvent	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
water	1.197	1.415	1.595	1.822	2.099
methanol	9.454	10.259	11.099	12.235	14.206
ethanol	1.531	1.843	2.109	2.441	2.840
1-propanol	1.436	1.712	1.960	2.282	2.642
2-propanol	1.338	1.551	1.819	2.142	2.429
1-butanol	1.382	1.641	1.909	2.194	2.566
1,2-propanodiol	19.730	20.624	22.031	23.228	25.083
2-ethoxyethanol	1.845	2.172	2.484	2.824	3.223
propanone	3.589	3.879	4.115	4.445	4.935
ethanonitrile	25.734	26.541	27.479	29.181	30.516
propanonitrile	3.924	4.156	4.401	4.769	5.259
propenonitrile	4.423	4.585	4.865	5.280	5.812

Table 3. Solubility Values in Molar Fraction Units X_s for BETABNEP in Each Solvent

	$X_s \times 10^3$				
solvent	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
water	0.038	0.057	0.077	0.099	0.115
methanol	2.887	3.267	3.805	4.455	5.341
ethanol	1.497	1.816	2.226	2.644	3.160
1-propanol	1.300	1.602	1.926	2.319	2.882
2-propanol	0.845	1.032	1.324	1.630	1.989
1-butanol	0.928	1.126	1.461	1.783	2.211
1,2-propanodiol	12.242	13.208	14.654	16.416	18.698
2-ethoxyethanol	2.558	2.972	3.476	4.103	4.799
propanone	2.749	3.080	3.633	4.247	4.948
ethanonitrile	3.071	3.499	4.211	4.884	5.718
propanonitrile	1.864	2.153	2.541	3.047	3.461
propenonitrile	5.915	6.614	7.426	8.556	10.376

Table 4. Enthalpy, Gibbs Energy, and Entropy of Dissolution of ATABNEP in Each Solvent, Assuming Ideal Behavior

	$\Delta H°$	$\Delta G°$	$\Delta S°$
solvent	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}·K^{-1}
water	43.4	−0.931	0.149
methanol	30.8	−11.0	0.140
ethanol	47.9	−2.16	0.168
1-propanol	47.6	−1.82	0.166
2-propanol	47.8	−1.42	0.165
1-butanol	48.2	−1.63	0.167
1,2-propanediol	18.9	−14.7	0.113
2-ethoxyethanol	43.5	−3.08	0.156
propanone	24.3	−6.30	0.103
ethanonitrile	13.7	−16.1	0.100
propanonitrile	22.8	−6.71	0.099
propenonitrile	21.6	−7.26	0.097

continuously during several days. (b) Samples were taken and weighed in a clean vial; afterward the vial was put into a vacuum oven where the solvents were evaporated at temperatures below 60 °C until constant weight of the solid was attained. (c) Step b was repeated until three solubility measurements coincided within 0.03%

At least three independent measurements of the solubility were performed for each salt−solvent pair. In all cases the repeatability was better than 0.05%. Mass measurements had an uncertainty of ±0.01 mg, while the amount of salt dissolved was always greater than 100 mg. Temperature was kept constant within ±0.05 °C.

Results and Discussion

Tables 2 and 3 show the measured solubility values for the two salts in the different solvents in molar fraction units at five temperatures.

Table 5. Enthalpy, Gibbs Energy, and Entropy of Dissolution of BETABNEP in Each Solvent, Assuming Ideal Behavior

	$\Delta H°$	$\Delta G°$	$\Delta S°$
solvent	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}·K^{-1}
water	87.4	15.4	0.241
methanol	48.5	−5.15	0.180
ethanol	60.3	−1.94	0.209
1-propanol	55.2	−1.62	0.191
2-propanol	68.4	0.877	0.227
1-butanol	69.3	0.435	0.231
1,2-propanediol	33.5	−12.3	0.154
2-ethoxyethanol	49.8	−4.61	0.183
propanone	47.2	−4.91	0.175
ethanonitrile	50.1	−5.47	0.186
propanonitrile	50.0	−3.04	0.178
propenonitrile	38.8	−8.91	0.160

From these data $\Delta H°$, $\Delta G°$, and $\Delta S°$ values for the dissolution of the salts in the different solvents were calculated, assuming ideal behavior, through the following relationships:

$$\partial \ln K_s/\partial T = \Delta H°/RT^2 \quad (1)$$

$$-RT \ln K_s = \Delta G° \quad (2)$$

$$\Delta G° = \Delta H° - T\Delta S° \quad (3)$$

where K_s is the solubility product of the salt. The resulting values are shown in Tables 4 and 5.

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Received for review September 26, 2001. Accepted September 14, 2002.

JE010263O