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Solvation and ion–ion interactions in aqueous and non-aqueous solutions of cationic cytostatic agent prospidium chloride

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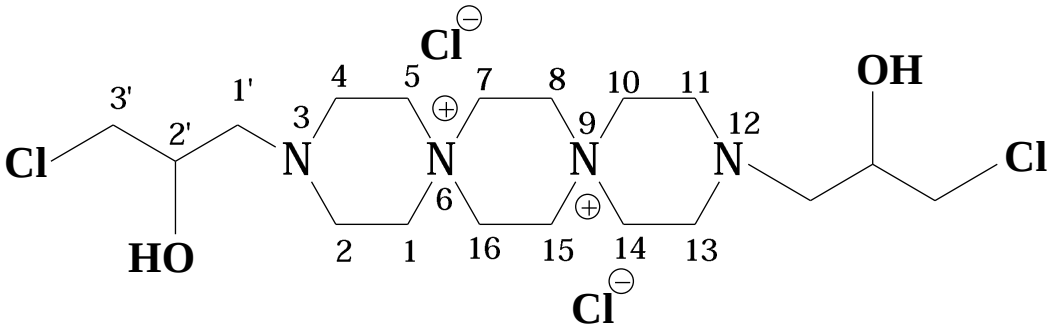
1. Identification and purification of prospidium chloride

The purity of prospidium chloride was confirmed by a number of techniques including IR, ^{1}H and ^{13}C NMR spectroscopy. All ^{1}H and ^{13}C NMR spectra of prospidium chloride were recorded on a Bruker Avance spectrometer (500 MHz) and given below.



^{1}H NMR (MeOD, 500 MHz), δ: 4.23 (br.m, 8H, 7,8,15,16-C$\underline{H}_2$-N^+), 4.10 (m, 2H, C$\underline{H}$-OH), 4.00 (br.m, 8H, 1,5,10,14-C$\underline{H}_2$-N^+), 3.72 (dd, 2H, *J* 5.4 and 11.2 Hz, C$\underline{H}_2^A$–Cl), 3.79 (dd, 2H, *J* 4.7 and 11.2 Hz, C$\underline{H}_2^B$–Cl), 3.12 (br.m, 8H, 2,4,11,13-C$\underline{H}_2$-N (cyclic)), 2.84 (dd, 2H, *J* 4.9 and 13.2 Hz, C$\underline{H}_2^A$–N (side chain)), 2.77 (dd, 2H, *J* 6.9 and 13.2 Hz, C$\underline{H}_2^A$–N (side chain)).

^{13}C NMR (MeOD, 500 MHz), δ: 46.11 (C$\underline{H}_2$–N (cycle)), 48.04 (C$\underline{H}_2$–Cl), 51.84, 59.82 (C$\underline{H}_2$–N(chain)), 69.21 (C$\underline{H}_2$–N^+).

^{1}H NMR (D_2O, 500 MHz), δ: 4.14 (br.m, 10H, 7,8,15,16-C$\underline{H}_2$–N^+, 2C$\underline{H}$–OH, 3.87 (br.m, 8H, 1,5,10,14-C$\underline{H}_2$–N^+), 3.74 (dd, 2H, *J* 3.6 and 11.8 Hz, C$\underline{H}_2^A$–Cl), 3.64 (dd, 2H, *J* 5.6 and 12 Hz, C$\underline{H}_2^B$–Cl), 3.05 (br.m, 8H, 2,4,11,13-C$\underline{H}_2$–N (cycle)), 2.72 (br.d, 4H, C$\underline{H}_2$–N (side chain), *J* 5.4 Hz).

^{13}C NMR (D_2O), 500 MHz), δ: 46.39 (C$\underline{H}_2$–N (cycle)), 48.32 (C$\underline{H}_2$–Cl), 52.17, 59.70 (C$\underline{H}_2$–N(side chain)), 68.27 (C$\underline{H}_2$–N^+).

Aqueous solutions of prospidium chloride were prepared immediately before the experiment due to a possible slow hydrolysis of the cation. Nevertheless, partial hydrolysis during the measurements seemed to take place since the ^{1}H NMR spectrum in water contain broader and less clear signals in comparison with the alcohol. It is worthy to note that pH value both before and after measurements was nearly identical of 6.2–6.3.

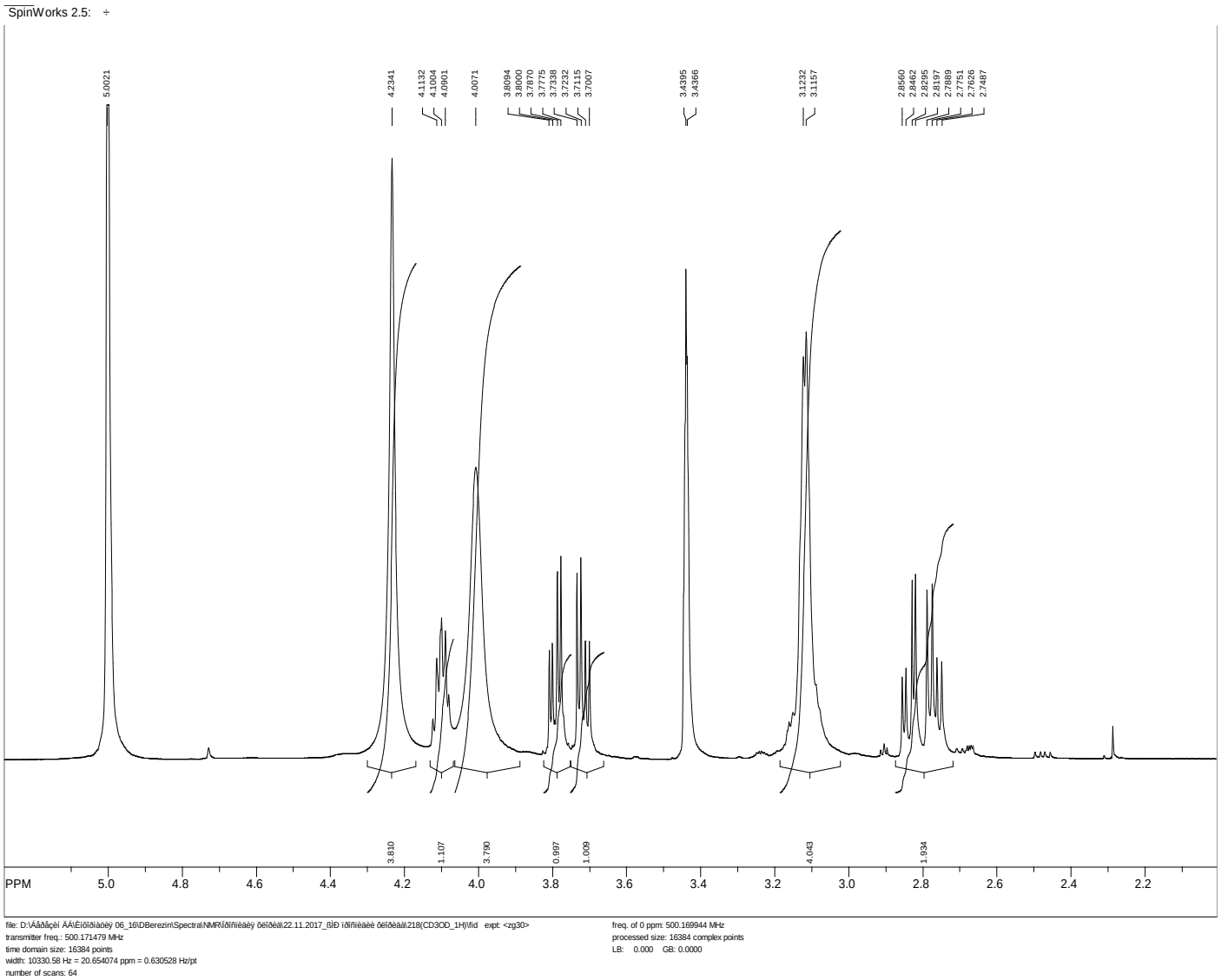


Figure S1 ^{1}H NMR spectrum of prospidium chloride in MeOD.

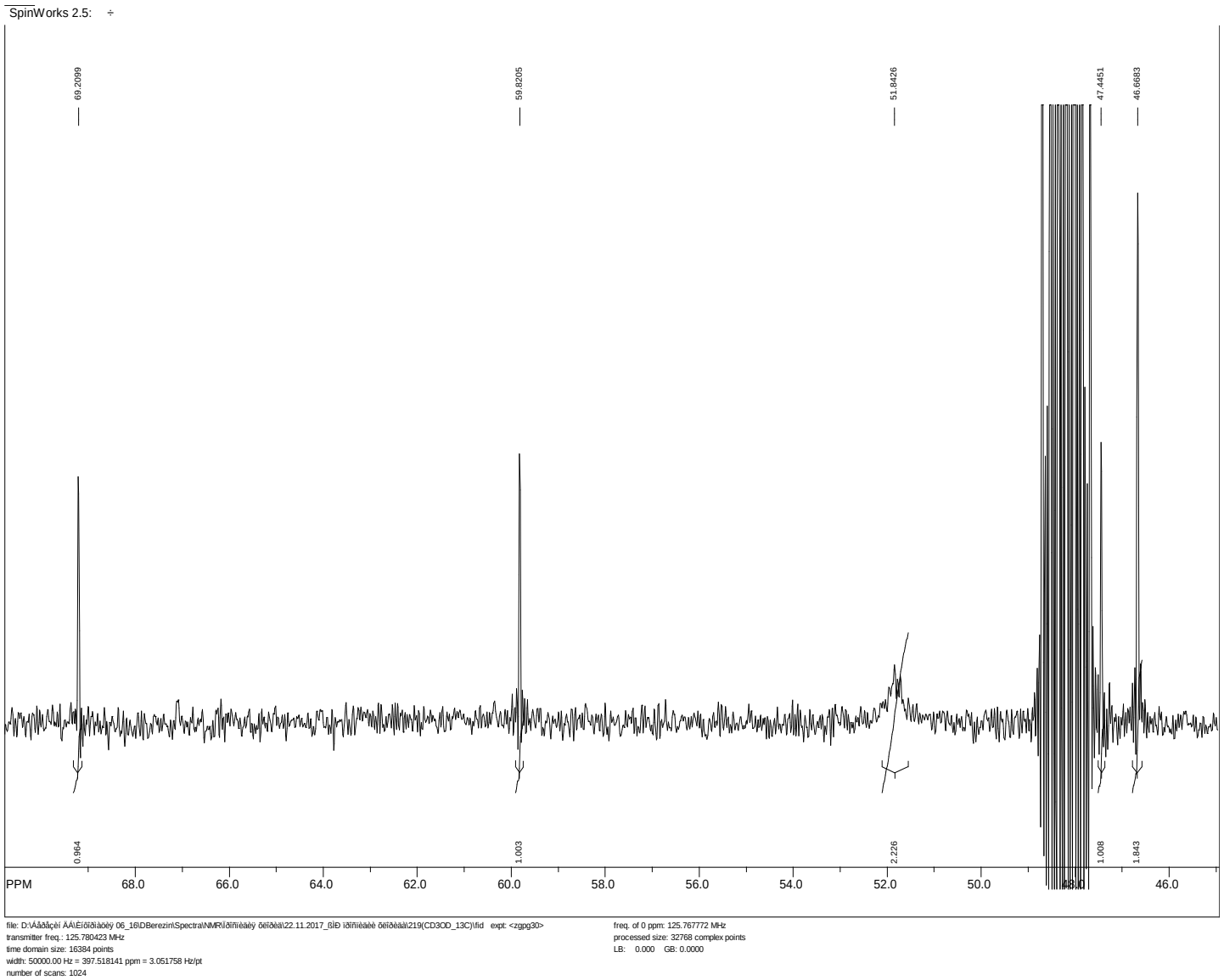


Figure S2 ^{13}C NMR spectrum of prospidium chloride in MeOD.

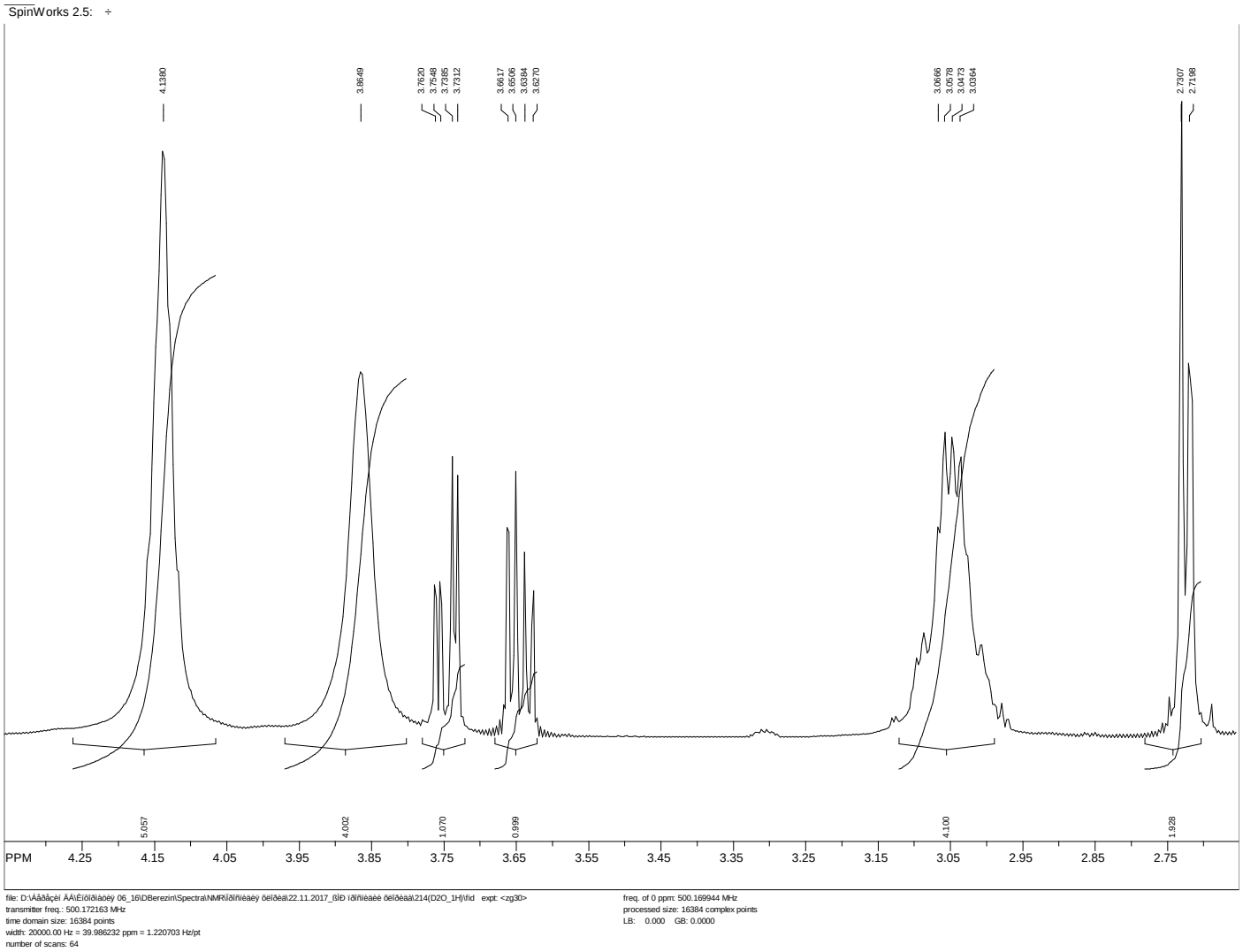


Figure S3 ^{1}H NMR spectrum of prospidium chloride in D_2O.

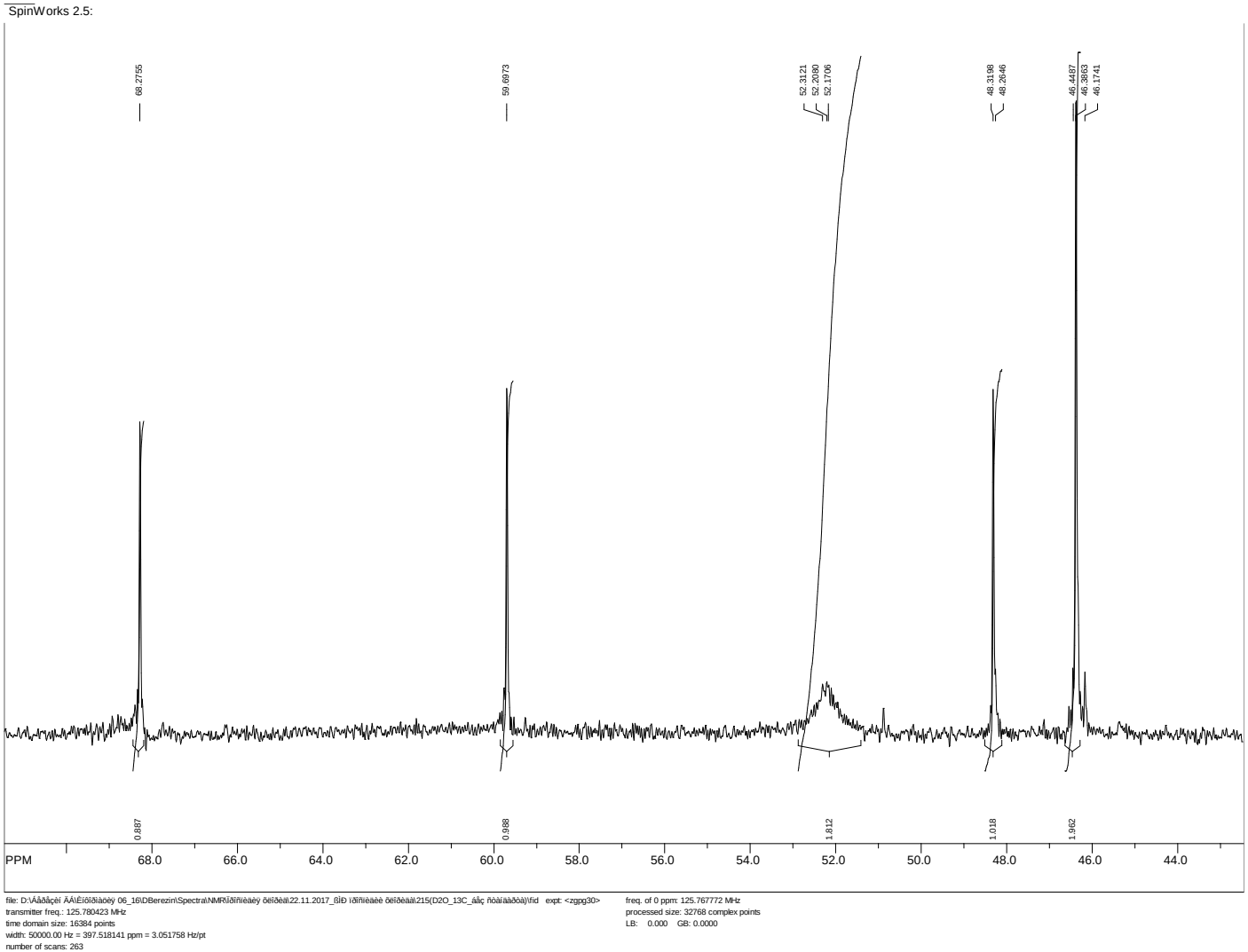


Figure S4 ^{13}C NMR spectrum of prospidium chloride in D_2O.

The IR-spectrum was recorded on 1n AVATAR 360 FT-IR ESP spectrophotometer. IR (KBr), ν/cm^{-1}: 3405 (OH), 2977 (CH–Cl), 2835 ($CH–NH_2$), 1470 (OH), 1326 (N–C), 1135 (C–OH), 1094 (C–Cl).

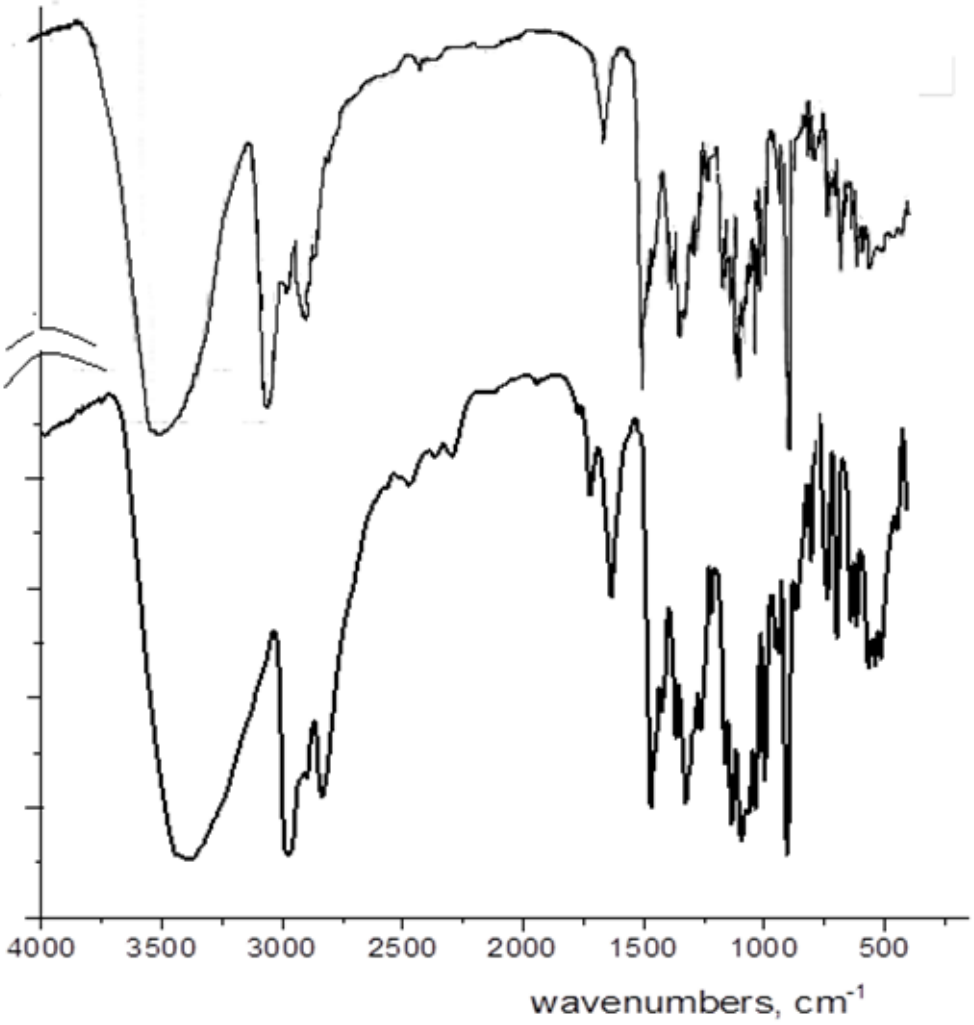


Figure S5 The comparison of IR-spectra of prospidium dichloride in KBr tablets: standard provided by the supplier (upper curve) and our sample (lower curve).

2. Chemicals

Prospidium chloride (Analytical grade, TNC biotechnological company, Moscow) was obtained from its dosage form and additionally dried *in vacuo* at ~338 K for two days. The final product was characterized with ^{1}H, ^{13}C NMR and IR spectra. Formamide (Panreac, >99%) and ethylene glycol (Aldrich, >99%) were dried over 4 Å molecular sieves and then distilled under reduced pressure at T = 353–358 K. Karl Fisher titration indicated that the water mass fraction in both liquids were 0.02 wt%.

3. Apparatus and methods

Calorimetric measurements were carried out on a precise isoperibol calorimeter fitted with a titanium vessel (70 ml) described in our previous works.[S1,S2] The detection limit of the apparatus was 10 μK. Heat effects were measured by a comparative method. An electrical calibration was carried out before and after the each experiment. Enthalpies of solution were corrected to the side effects associated with an ampoule crushing on the vessel bottom. Duration of prospidium chloride dissolution in our calorimetric cell was of five minutes in both solvents.

4. Results

Experimental and standard enthalpies of solution at 298.15 and 313.15 K are listed in Table S1.

Table S1 Experimental ($\Delta_{sol}H^m$) and standard ($\Delta_{sol}H^0$) enthalpies of solution of prospidium chloride in ethylene glycol and formamide at 298.15 and 313.15 K

T = 298.15 K		T = 313.15 K	
m^a/mol kg^{-1}	$\Delta_{sol}H^m$/kJ mol^{-1}	m/mol kg^{-1}	$\Delta_{sol}H^m$/kJ mol^{-1}
		Ethylene glycol	
0.00091	3.14	0.00104	5.19
0.00095	3.17	0.00141	5.32
0.00203	3.55	0.00208	5.62
0.00223	3.71	0.00396	6.14
0.00306	4.07	0.00562	6.47
0.00367	4.26	0.00711	6.78
0.00430	4.53	$\Delta_{sol}H^0$ = 3.41±0.11^b	
0.00500	4.76		
$\Delta_{sol}H^0$ = 1.61±0.14			
		Formamide	
0.00262	2.97	0.00209	3.96
0.00528	2.93	0.00400	3.99
0.00739	2.90	0.00594	4.00
0.00973	2.89	0.00754	3.98
$\Delta_{sol}H^0$ =2.96±0.04		0.00882	4.02
		$\Delta_{sol}H^0$ = 3.86±0.04	

[a] Herein m denotes molality of prospidium chloride.
[b] Uncertainties for the experimental quantities represent the twice standard deviation.

5. References

S1 A.V. Kustov, O.A. Antonova, N.L. Smirnova, A.A. Kladiev, A.A. Kladiev, T.V. Kudayarova, M.S. Gruzdev, D.B. Berezin, *J. Mol. Liq*. 2018, **263**, 49.

S2 A.V. Kustov, O.A. Antonova, N.L. Smirnova, I.S. Khudyaeva, D.V. Belykh, D.B. Berezin, *Thermochim. Acta*, 2018, **669**, 169.