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Hydrogen bonds determine the signal arrangement in ¹³C NMR spectra of nicotinate

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¹³C-¹H HSQC spectrum of nicotinate (0.25 mol kg⁻¹, aqueous)

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1	ACCEPTED MANUSCRIPT Hydrogen bonds determine the signal arrangement in ¹³ C NMR
2	spectra of nicotinate
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11	Present work reports on studies of sodium nicotinate solutions in water and aqueous ethanol by
12	means of ¹ H, ¹³ C, ¹⁵ N NMR spectroscopy. The H(2) nucleus was observed to be the least
13	shielded among pyridine ring protons whilst C(6) signal placed in the lowest field in relation to
14	the other pyridine carbons. The hydrogen bonds formation between nicotinate and water
15	molecules was shown to be probable reason of signal arrangement in ¹³ C NMR spectra of
16	nicotinate. The heteronitrogen of nicotinate is less prone to the hydrogen bonding with water
17	molecules than that of nicotinamide. The data on the change in the Gibbs energy of the nicotinate
18	transfer and the results of the 13C NMR experiment are compared.
19	
20	Keywords: nicotinate, HMBC ¹⁵ N- ¹ H, HSQC ¹³ C- ¹ H, NMR, hydrogen
21	bond, aqueous ethanol
22	
23	1. Introduction
24	Pyridine-3-carboxylic acid (nicotinic acid, PP or B ₃ vitamin) is a vitamin of
25	B group and drug used as pellagra treating, preventing remedy, and lipid-lowering
26	agent, which could be used in complex therapy of atherosclerosis, hyperlipidemia,
27	insulin resistance [1-3]. Nicotinic acid acts as precursor of nicotinamide adenine
28	dinucleotide (NAD) coenzyme in living organisms [4].
29	Moderately soluble in water [5], nicotinic acid could be administered as
30	calcium or sodium salts [6]. At the physiological pH value of 7.4, the anionic

species of nicotinic acid could only exist [7]. Due to that, nicotinate solvation in

ACCEPTED MANUSCRIPT water or in water mixtures with ethanol, a solvent, widely used in medicine, is of 1 2 interest for researchers.

3 Recently, a number of papers describing the behavior of different aqueous solutions of nicotinic acid had appeared. For example, authors [8] found that either 4 nicotinic acid or nicotinate keeps primary solvation sphere in aqueous solutions of 5 sodium gluconate. The hydrophobic hydration is the predominant interactions type 6 in such a system [8]. B. Sinha's group noted the nicotinic acid in aqueous solutions 7 of sodium malonate to act as structure-promoting agent [9]. Analogous conclusions 8 had been made in report [10] describing the aqueous solutions of nicotinic acid and 9 10 some other vitamins. The complex character of solute-solvent and solute-solute interactions in the systems containing nicotinic acid was observed [11]. The 11 12 standard molar enthalpies of nicotinic acid dissolution and nicotinate formation in 13 water were determined [12].

The solvation state of nicotinic acid vitamer, nicotinamide, in mixed 14 aqueous-organic solvents had being studied [13, 14]. The authors [15] focused on 15 the study of the hydrogen bonds (H-bonds) between nicotinamide and water and π -16 π stacking between nicotinamide molecules. 17

The present work reports on the influence of the aqueous ethanol solvent 18 composition on ¹³C NMR spectrum of nicotinate (NA⁻). ¹H, ¹⁵N NMR experiments 19 are also discussed. We focus on the reasons determining the signal arrangement in 20 21 NMR spectra combining both experimental and quantum chemical methods.

22

2. Experimental

Nicotinic acid (Merck Millipore, Germany) was used without additional 23 purification. The purity of the reagent claimed by manufacturer was >99.9 % 24 (weight). The aqueous or aqueous ethanol solutions of sodium nicotinate for NMR 25 studies were prepared by adding the exact quantity of preliminarily standardized 26 NaOH solution to the 0.249-0.251 mol kg⁻¹ nicotinic acid solution. The bidistilled 27 water (pH = 6.6, $\kappa = 1.7 \ \mu \text{Sm cm}^{-1}$) was used for every solution preparation. The 28 ethanol was distilled under atmospheric pressure. Water content in the ethanol was 29

controlled densimetrically (4.56 weight %) and was taken into account when the
 binary solvents were made by the weighting of the accurate amounts of water and
 organic solvent with inaccuracy 0.0002 g.

The ¹H-¹⁵N HMBC, ¹H-¹³C HSQC, ¹³C NMR spectra of sodium nicotinate 4 solutions $(0.249-0.251 \text{ mol kg}^{-1})$ in water and aqueous ethanol were recorded on 5 Avance III Bruker 500 NMR spectrometer with operating frequencies of 500.17, 6 125.77, 50.701 MHz (¹H, ¹³C, ¹⁵N nuclei respectively) at the temperature of 298.2 7 K. A 5 mm 1H/31P/D-BBz-GRD triple resonance broad band probe (TBI) was 8 employed. Nitromethane and hexamethyldisiloxane were used as external 9 standards for ¹⁵N and ¹H, ¹³C nuclei respectively. An experimental error of 10 chemical shift measuring did not exceed 0.005 ppm for ¹³C, and 0.1 ppm for ¹⁵N. 11 The accuracy of temperature maintaining using temperature unit BVT-3000 was 12 13 ± 0.1 K. Some spectra are given (Figs. S1-S6).

Quantum chemical calculations were performed using Firefly QC package 14 [16], which is partially based on the GAMESS (US) source code [17]. The 15 functional B3LYP [18] (DFT method) with basis set 6-311++G(d,p) [19] was 16 chosen to optimize the geometry of nicotinate H-complexes. The basis set choice is 17 justified by its successful application towards analogous compounds in previous 18 19 studies [20-22]. The suggested ground states were verified by frequency analysis after optimization. NMR chemical shifts (GIAO [23]) were calculated at the same 20 21 theory level and referenced to the preliminarily calculated chemical shifts of benzene [24] as proposed in [25]. The solvent (water) was set within the 22 framework of CPCM approach in all cases. 23

24

3. Results and Discussion

In the ¹H NMR spectrum of aqueous solution of sodium nicotinate, there are four signals referring to the studied compound. They could be assigned uniquely using spin-spin coupling constants (Fig. S1).

The proton of site 2 has no neighboring C-H groups, therefore its signal is slightly split (dd, ${}^{4}J_{2,4} = 1.72$ Hz, ${}^{5}J_{2,5} = 0.96$ Hz). The H(6) resonance is split more

1 (dd, ${}^{3}J_{6,5} = 4.98$ Hz, ${}^{4}J_{6,4} = 1.72$ Hz). The rest hydrogen peaks are also significantly 2 split (H(4): dt, ${}^{3}J_{4,5} = 7.85$ Hz, ${}^{4}J_{4,6} = 1.72$ Hz; H(5): ddd, ${}^{3}J_{5,4} = 7.85$ Hz, 3 ${}^{3}J_{5,6} = 4.98$ Hz, ${}^{5}J_{2,5} = 0.96$ Hz). As expected, H(2) signal is shifted towards lower 4 field in relation to the other protons of aromatic system.

5 The carbon signals in the ¹³C NMR spectrum could be anticipated to follow 6 in the same order. However, it is the C(6) nucleus that is the least shielded one 7 among the pyridine ring carbons as it follows from ¹³C-¹H HSQC experiment 8 results (Fig. S2). Nicotinamide was also reported to possess the same order of 9 signals in the ¹³C NMR spectrum ($\delta_{C6} > \delta_{C2} > \delta_{C4} > \delta_{C5}$) [13, 14], however, to the 10 best of our knowledge, no explanation had been given yet.

Unlike the experiment, the quantum chemical calculations of NMR spectrum of nicotinate taking into account the solvent, water (PCM), show C(2) as the least shielded nucleus (See Figs. S8-S15 and Table 1) in all cases except for S15 (nicotinate+40 water molecules).

15

16 **Table 1**. Calculated NMR spectra of models S8-S15 (nicotinate + n water

17 molecules), MAE (Mean Absolute Error^{*}) values and correlation coefficients

18	between	calculated	and	experimental	chemical	shifts

Model	S 8	S9	S10	S11	S12	S13	S14	S15	
Number									Fyn
of water	0	1	1a	2	3	6	8	40	Exp.
molecules									
H(2)	8.84	8.88	8.86	8.75	8.81	8.95	8.85	8.87	8.12
H(6)	8.16	8.11	8.23	8.17	8.21	8.21	8.21	8.60	7.79
H(4)	7.98	8.06	8.01	8.06	8.08	8.11	8.13	8.25	7.43
H(5)	6.90	7.00	6.94	6.82	7.04	7.03	7.05	6.97	6.70
MAE	0.46	0.50	0.50	0.44	0.53	0.57	0.55	0.66	
$R^2_{adj.}^{**}$	0.9617	0.9193	0.9725	0.9451	0.9556	0.9380	0.9399	0.9544	
Model	S 8	S 9	S10	S11	S12	S13	S14	S15	Evn
Nucleus	0	1	1a	2	3	6	8	40	Exp.
C(7)	169.10	168.74	170.14	169.20	169.90	170.88	170.29	177.69	172.16
C(6)	151.09	148.75	151.59	149.57	149.98	150.49	150.44	152.11	149.40
C(2)	152.39	150.83	152.50	150.42	150.65	151.03	150.89	153.33	148.02
C(4)	137.05	138.11	137.35	138.88	139.06	138.82	139.15	142.43	136.65
C(3)	134.79	134.88	133.80	134.68	134.03	133.15	133.22	129.63	131.26
C(5)	122.33	123.00	122.63	123.25	123.25	123.55	123.32	123.45	122.90
$\delta_{C(2)}$ - $\delta_{C(6)}$	1.30	2.08	0.91	0.85	0.67	0.54	0.45	-1.22	-1.38

			Δ	CCEPT	ED MAI	NILISCR	IPT			
	MAE	2.27	2.01	2.03	1.92	1.83	1.68	1.78	3.31	
	$\mathbf{R}^{2}_{\mathrm{adj.}}^{**}$	0.9705	0.9812	0.9785	0.9864	0.9891	0.9926	0.9903	0.9840	
	* $MAE = \frac{\sum_{i=1}^{n}}{\sum_{i=1}^{n}}$	$\sum_{1} \left \delta_{\text{exp}} - \delta \right $	calc _i							
п										

 ${}^{**}R^{2}_{adi}$ - adjusted R-squared (number of variables = 1)

3

2

Adding the water molecules forming hydrogen bonds (H-bonds) with 4 5 nicotinate results in the change of difference between C(2) and C(6) chemical shifts. Water specifically interacts with nicotinate nitrogen and causes the 6 increasing of δ_{C2} - δ_{C6} , thus, increasing the difference between experimental and 7 calculated NMR spectra. On the contrary, water binding with -COO⁻ group 8 decreases the difference of δ_{C2} - δ_{C6} (See Table 1). The greater the number of water 9 molecules added to the nicotinate in the model, the closer the calculated values of 10 C(2) and C(6) chemical shifts become. Eight water molecules added to the 11 nicotinate decreases the difference of δ_{C2} - δ_{C6} to 0.45 ppm (see Table 1). Finally, 40 12 water molecules added to the nicotinate makes the calculated ¹³C NMR signals 13 14 order to be in agreement with experimental results (Table 1). Suggesting the model S15, which contains 40 water molecules, we aimed to form the first solvation shell 15 16 surrounding uniformly the nicotinate.

The geometry of pyridine residue of nicotinate is slightly disturbed by water 17 molecules added. In the S8 structure (CPCM only) the bond lengths values are 18 indicative of conjugated structure (C-C distances of 1.39-1.40 Å, C-N distances of 19 1.34 Å) [26]. Adding from 1 to 8 molecules changes the bond lengths in the 20 heterocycle by 0.001-0.002 Å, while the transfer from S14 to S15 structure gives 21 also 0.001-0.002 Å variation to bond lengths. The C_3 - C_7 undergoes the most 22 significant shortening: from 1.533 Å in S7 to 1.503 Å (40 water molecules added). 23 The C-O bond lengths also change noticeably. Being equivalent in the S8 model 24 (1.258 Å), they become slightly unequal and longer in S15 structure (1.266 Å and 25 1.269 Å). The hydrogen bond between nitrogen and water proton elongates from 26 1.839 Å (S9) to 1.850 Å (S15), while the quantity of water molecules increases. In 27

the models \$10-\$14, carboxylate oxygens form two H-bonds with water with bond
lengths of 1.7-1.8 Å. When 40 water molecules are added to nicotinate, a number
of H-bonds between COO⁻ group and solvent molecules could be suggested basing
on the interatomic distances range of 1.8-2.0 Å.

The H-bonds formed between water and nicotinate nitrogen are probably 5 weaker than in case of nicotinamide heteronitrogen. This suggestion could be 6 confirmed either using quantum chemical calculations of ¹³C NMR spectra (adding 7 the water molecule H-bonded with nitrogen increases difference between 8 calculated and experimental spectra) or comparing the ¹⁵N-¹H HMBC spectrum of 9 aqueous solution of nicotinate with that of nicotinate dissolved in aqueous ethanol 10 $(X_{EtOH} = 0.7)$. The difference between nitrogen chemical shifts of nicotinate in two 11 solvents ($\delta_N = -85.2$ ppm at $X_{EtOH} = 0$, $\delta_N = -83.4$ ppm at $X_{EtOH} = 0.7$) is less than 12 that of nicotinamide ($\delta_N = -78.5$ ppm at $X_{EtOH} = 0$, $\delta_N = -74.1$ ppm at $X_{EtOH} = 0.7$ 13 14 [13]).

Taking all above into account, the order of signals in experimental ¹³C NMR spectrum of nicotinate (aqueous solution) could be concluded to be determined by H-bond formation between –COO⁻ group of solute and the large quantity of water molecules surrounding the nicotinate.

The analysis of dependencies of C(2) and C(6) chemical shifts on ethanol
concentration in the binary solvent confirms that suggestion (Fig. 1).



1

Figure 1. Dependencies of C(2), C(6) and C(7) chemical shifts on aqueous
ethanol solvent composition

Alcohol content growth leads to the decreasing of water molecules quantity 5 capable of H-bonding the nicotinate (either nitrogen and ionized carboxylic group). 6 By this reason, the signals of C(2) and C(6) become closer until ethanol 7 concentration ca. 0.47 mole fraction and, being swapped, diverge at higher alcohol 8 content (Fig. S3). It is worth noting that the same order of ¹³C NMR peaks (δ_{C2}) 9 $\delta_{C6} > \delta_{C4} > \delta_{C5}$) is observed also in aqueous DMSO and aqueous DMF (both $X_{H2O} =$ 10 0.3, see Figs. S4, S5), which also could confirm the influence of H-bonds with 11 water on the signal arrangement in the ¹³C NMR spectrum of nicotinate. 12

The tendency of C(2) and C(6) carbons to converge at the increasing of ethanol concentration was observed also in case of nicotinamide [27]. However, the C(2) and C(6) peaks of nicotinamide had never swapped due to higher distance between resonances (>4 ppm in water) and their unidirectional shift.

17 All the dependencies of nicotinate carbon chemical shifts on ethanol content 18 presented bend slightly at $X_{EtOH} = 0.2-0.35$ m.f. (Fig. 1). The most significant

changes of nicotinate solvation state probably occurs in that interval of binary 1 2 solvent composition.

The significant growth of Gibbs energy change of nicotinate transfer 3 accompanies the decreasing of water molecules quantity capable of H-bonding the 4 solute (Fig. 2). 5

6



Figure 2. The Gibbs energy changes of nicotinate transfer from water to 8 aqueous ethanol 9

10

7

The Gibbs energy change of nicotinate transfer from water to ethanol 11 $\Delta_{tr}G(NA^{-})$ is defined as follows: 12

13
$$\Delta_{tr}G(NA^{-}) = \Delta G(NA^{-})_{H2O-EtOH} - \Delta G(NA^{-})_{H2O}$$
(1);

where $\Delta G(NA^{-})_{H2O-EtOH}$ is the Gibbs energy change of nicotinate solvation in 14 15 the binary solvent of water-ethanol; $\Delta G(NA)_{H2O}$ is the Gibbs energy change of nicotinate solvation in water. 16

 $\Delta_{tr}G(NA^{-})$ (Fig. 2) is calculated basing the data on Gibbs energy change of 17 transfer of dissociation reaction ($\Delta_{tr}G_r$) of nicotinic acid (HNA): 18

19
$$\Delta_{tr}G(NA^{-}) = \Delta_{tr}G_{r} - \Delta_{tr}G(HNA) - \Delta_{tr}G(H^{+})$$
(2);

1 The values of $\Delta_{tr}G_r$ and $\Delta_{tr}G(H^*)$ are taken from papers [7] and [28] 2 respectively. $\Delta_{tr}G(HNA)$ is calculated using report [29] data considering the 3 tautomeric equilibria of nicotinic acid:

4

 $\Delta_{tr}G(HNA) = X_{+} \cdot \Delta_{tr}G(HNA_{+}) + X_{0} \cdot \Delta_{tr}G(HNA_{0})$ (3);

where X_{\pm} , X_0 are the mole fractions of zwitterionic and neutral species of nicotinic acid, $\Delta_{tr}G(HNA_{\pm})$, $\Delta_{tr}G(HNA_0)$ are Gibbs energy changes of zwitterionic and neutral species transfer.

8 Therefore, the increasing of ethanol concentration in the binary solvent leads 9 to H-bonds breaking between water and nicotinate, and nicotinate is solvated less 10 efficiently.

11

4. Conclusions

There are four signals referred to pyridine residue in the ¹H NMR spectrum 12 of aqueous solution of sodium nicotinate. They are placed in the following order: 13 $\delta_{H2} > \delta_{H4} > \delta_{H4} > \delta_{H5}$. The different order of signals is observed in ¹³C NMR spectrum 14 of nicotinate ($\delta_{C6} > \delta_{C2} > \delta_{C4} > \delta_{C5}$). Hydrogen bonds formed between water molecules 15 and $-COO^{-}$ group of solute are the most probable reason for C(6) carbon peaks 16 shifted towards lower field in relation to other nuclei of pyridine ring. From the 17 18 one hand, this suggestion is confirmed by quantum chemical calculations results showing the tendency of C(2) and C(6) resonances to converge at water molecules 19 adding to the model. Accounting the solvation shells of solutes is important for 20 21 obtaining the correspondence between calculated and experimental data. Modelling the solvation shell of nicotinate using 40 water molecules (model S15) leads to 22 agreement between experimental and calculated signals order. From the other 23 hand, ¹³C NMR study of aqueous ethanol solutions of sodium nicotinate show the 24 C(2) and C(6) signals swapped at the ethanol concentration of 0.4-0.45 m.f., which 25 makes the order to be $\delta_{C2} > \delta_{C6} > \delta_{C4} > \delta_{C5}$. The same signal arrangement is also 26 observed in the solutions of nicotinate in aqueous DMSO ($X_{DMSO} = 0.7$) and 27 aqueous DMF ($X_{DMF} = 0.7$). 28

The dependencies of C(7), C(6), C(2) nuclei chemical shifts on aqueous ethanol solvent composition bend slightly at $X_{EtOH} = 0.2-0.35$ m.f. Probably, the most significant changes of solvation state of nicotinate occur within this range of ethanol concentrations.

Nicotinate heteronitrogen is probably less H-bonded with water molecules than that of nicotinamide. Adding the water molecule H-bonded with nitrogen of nicotinate increases the difference between calculated and experimental ¹³C NMR spectra. Small changes of ¹⁵N chemical shift (*ca.* 1.4 ppm) while nicotinate transfers from water to aqueous ethanol ($X_{EtOH} = 0.7$) also confirm this suggestion.

10 Decreasing the water molecules quantity capable of H-bonding the 11 nicotinate is accompanied by the increasing of Gibbs energy change of nicotinate 12 transfer from water to aqueous ethanol.

13

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- Signals order in ¹H, ¹³C NMR spectra of nicotinate is different;
- It is caused by hydrogen bonds formation between water and -COO⁻ group;
- H-bonds between nicotinate nitrogen and water are weak;
- Aqueous ethanol solvent composition influence on nicotinate NMR is studied.