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¹H and ¹⁷O NMR study of H-bond dynamics in picolinic acid *N*-oxide solutions in acetonitrile- h_3 and acetonitrile- d_3 : novel aspects of old casus

Arūnas Maršalka¹, Laurynas Dagys¹, Virginija Jakubkienė², Sigitas Tumkevičius², Vytautas Balevicius^{1*}

¹Institute of Chemical Physics, Vilnius University, Sauletekio av. 3, LT-10257 Vilnius, Lithuania ²Institute of Chemistry, Vilnius University, Naugarduko str. 24, LT-03225 Vilnius, Lithuania

Abstract

Despite apparent similarity, two isotopomers of acetonitrile (ACN- h_3 and ACN- d_3) show unexpected differences in their structural and dynamic properties. These differences cannot be fully understood within the usual isotope effect and therefore called as unresolved casus. Sensing the solvent properties, the H-bond dynamics of picolinic acid *N*-oxide (PANO) in ACN was studied using ¹H and ¹⁷O NMR. Several overlapping factors, like the presence of micro-traces of water, liquid-liquid equilibrium, effect of ionic ingredient, etc., which may cause the observed anomalies in the dependences of PANO chemical shift and signal width on temperature, were analyzed. The deuterium isotope effect on the phase separation in organic solute/water mixtures was deduced to be the crucial factor inducing those surprising differences between ACN- h_3 and ACN- d_3 . Thus the casus could be resolved within the second-order phase transition model, in which the vibrational contributions to the intermolecular interaction energies would be properly taken into account.

Keywords: NMR spectra; hydrogen bond; isotopic effects; liquid-liquid phase separation; phase transitions

^{*}Corresponding author. E-mail address: <u>vytautas.balevicius@ff.vu.lt</u> (V. Balevicius).

1. Introduction

Acetonitrile (CH₃CN, ACN) is a widely used solvent or co-solvent, in which many hydrophobic, hydrophilic and ionic materials can be dissolved [1]. ACN-water mixtures exhibit anomalous thermodynamic properties and complex structures with the regimes of microheterogeneity dependent on concentration and temperature ([1] and Refs cited therein). In separation science (liquid - liquid and solid - phase extraction) ACN plays a key role as an extraction medium [2]. Therefore, the molecular systems containing ACN as one of the components have been widely studied with particular emphasis on the structure, intermolecular interactions, vibrational and orientational dynamics.

Two isotopomers of acetonitrile (ACN- h_3 and ACN- d_3) were studied in a series of works using IR, Raman and depolarized Rayleigh scattering in order to elucidate their dynamic behavior and determine their local structural organization [3-6]. The unusual behavior was revealed analyzing the IR and Raman spectra of C–H/C–D symmetric stretching and CH₃/CD₃ symmetric bending vibrations of the pure ACN, equimolar isotopic mixtures and equimolarly diluted in CCl₄. The general conclusion emerging from those works was that despite their apparent similarity, ACN- h_3 and ACN- d_3 show unusual and surprising differences in their structural and dynamic properties, which are not fully understood within the usual isotope effect.

Another group of works deal with electronic processes, like charge transfer reactions [7], resonance Raman scattering and fluorescence of dye molecules [8-10], which occur in the solutions of ACN- h_3 and ACN- d_3 . No effects from solvent isotope substitution on the reaction rate and reaction yield have been found in the case of the intramolecular charge transfer in 4-(1-azetidinyl) benzonitrile [7]. However, the Raman cross sections of betaine-30 were found in ACN- d_3 to be lower than those in ACN- h_3 , and different solvent reorganization energies were determined [8,9]. Probably the most interesting results have been obtained in Ref. 10 studying the solvation dynamics of dye molecules in methanol and ACN. The effects of solvent deuterium substitution on

the fluorescence spectra and the time domain data were found to be significant in both solvents. The ultrafast components (~200–260 fs) were found to be not sensitive to the deuterium substitution. Beside the components in ultrafast (fs and ps) solvation time scale, a large amplitude component in the scale of nanoseconds was observed in both solvents. The amplitudes of this component are substantially different in isotopomers, showing the opposite trend in ACN and methanol [10].

In summary, the different experimental trends shown by the normal and deuterated solvents can be not always explained by a regular dynamic isotopic effect, i.e. their kinetic/transport coefficients to be proportional to the square root of the ratio between the isotopomer masses [3]. In Ref. 6 this was called as an unresolved casus. In the current work we present a complementary NMR observation of non-trivial effect of isotopomers of acetonitrile, as reaction media, on the intramolecular hydrogen bond (H-bond) dynamics in picolinic acid *N*-oxide. The obtained results can be understood accepting that the isotopic substitution of solvent molecules drastically influents the micro-structuring and the local fluctuation processes culminating with liquid-liquid phase transition (phase separation) therein.

2. Experimental

Commercial picolinic acid *N*-oxide (PANO), 97 %, from Sigma-Aldrich was dried keeping for 2 days under vacuum at ~ 380 K. Acetonitrile (ACN- h_3), anhydrous, 99.8 % (I) and deuterated acetonitrile (ACN- d_3), \geq 99.8 atom % D (II), both from Sigma-Aldrich and ACN- h_3 , LC-MS, \geq 99.9 % (III) from Fluka have been used as solvents preparing the samples on two different levels: a) the preparation under ambient conditions – i. e. without using of vacuum techniques, molecular sieves and without keeping a sample closed in a dry environment during all stages of preparation (weighting of components, tube filling, etc.); b) the high-level preparation - all stages

run in a glove-box filled with extremely dry nitrogen (humidity ≤ 0.1 ppm) and in some cases keeping ACN over the molecular sieves (3 Å) for several days before.

The 4-nitro derivative of PANO (4-nitro-PANO) was synthesized in the Department of Organic Chemistry of Vilnius University by nitration of PANO using a slightly modified procedure than that reported in [11]. A mixture of 2-picolinic acid N-oxide (1 g, 6.36 mmol), conc. H_2SO_4 (3 mL), and conc. HNO_3 (2.2 mL, d = 1.5 g/cm³) was heated at 408 K under stirring for 3 hr. After cooling to room temperature, the reaction mixture was poured to a crushed ice. The formed precipitate was filtered off, washed with water till pH = 7 and recrystallized from ethanol to give 0.4 g (31%) of 4-nitropicolinic acid *N*-oxide, m.p. 422 – 423 K, Ref. 11: m.p. 421 K. The solutions were prepared by weighting (± 0.1 mg) the components.

¹H and ¹⁷O NMR experiments were carried out on a BRUKER AVANCE III 400 WB NMR spectrometer operating at 400 and 54 MHz for ¹H and ¹⁷O, respectively, using BBO probe-head. The variable-temperature measurements in the range of 230 K - 350 K were controlled with the accuracy of \pm 0.5 K. The signal of TSPSA (3-(trimethylsilyl)propane sulfonic acid sodium salt) in ACN-*d*₃ solution in capillary insert was used as the reference for ¹H NMR spectra and for lock. The D₂O in the capillary insert was used for reference in ¹⁷O NMR spectra. In order to get better signal-to-noise ratio the natural abundance ¹⁷O spectra were recorded using 10 mm tubes. The $\pi/2$ pulses of 22.5 μ s at the transmitter power of 70 W were applied using the acquisition time of 0.02 s and the recycle delay of 0.4 s. The number of scans was 400000. When necessary, ¹H and ¹³C chemical shifts of PANO were confirmed by the analysis of 2D homo-and hetero-nuclear NMR experiments (¹H–¹H COSY, ¹H–¹³C HSQC and ¹H–¹³C HMBC). NMR spectra were processed using Topsin 3.2 software. Additionally, the signal shapes were processed using *Microcal Origin* 9 package.

3. Results and discussion

The NMR experiments have been performed in wide temperature range approaching the melting (M.P.) to boiling (B.P.) points of ACN (227 - 232 K and 354 K, respectively [2,12]). This was because the warning given in [6] that no anomalies could be evidenced in the isotopic dilution experiments if experiments are carried out at the fixed temperature.

PANO was chosen for the study because of several reasons. The H-bond complexes between carboxylic acids and pyridine N-oxide or its derivatives are promising benchmark systems for short O-H...O hydrogen bonding [13]. These systems exhibit in most cases asymmetric and flat single well proton potentials, which result in large-amplitude proton dynamics that often culminates with occurrences of proton transfer (PT). PANO is maybe the most prominent member of this family [13]. Quantum mechanical simulation of the proton dynamics by Car-Parrinello method shows that the H-bond proton in crystalline PANO is located about 99% of time in the energy minimum near the carboxylic oxygen (O1) and the jumps to the N–O(3) acceptor are rare (for atom numbering see Fig. 1) [14]. However, the H-bond in PANO in liquid solutions looks to be more soft and flexible. Even the solvent effect is clearly pronounced on the proton potential functions at increasing polarity of the solvents [15]. Thus, a large amplitude motion of the H-bond proton in PANO, including PT process, could be expected in ACN solutions. And indeed, the ¹⁷O NMR spectrum of PANO dissolved in ACN- h_3 confirms that the fast (in the sense of NMR time scale, i.e. $\sim 10^{-5}$ -10⁻⁶ s) intramolecular H-bond proton dynamics coupled with the interchange of O1 and O2 oxygen atoms occurs in this system (Fig. 1). The probable scheme for such interchange is shown in Fig. 1. It is the intramolecular process and could be realized if PT from O1 to O3 atoms occurs. The intermolecular exchange could run too, however, if PANO molecules formed the cyclic dimers or even higher H-bond aggregates. In order to confirm or to deny the possibility of the intermolecular route, PANO was mixed with one of its derivatives - 4-nitro-PANO, and ¹H NMR spectra were registered.



Fig. 1. Natural abundance ¹⁷O NMR spectrum of PANO dissolved in ACN- h_3 confirming a fast intramolecular H-bond proton dynamics with sequent interchange of O1 and O2 oxygen atoms (0.3 M, T = 293 K).

Because of the limited solubility of PANO and its derivatives in ACN only ~ 0.3 M concentration was achieved. Two separated signals of H-bond protons are seen in the ¹H NMR spectrum of PANO mixed with 4-nitro-PANO and dissolved in ACN- h_3 (Fig. 2). This means that at such relatively high dilution the intermolecular H-bond exchange does not occur at all or it is very slow. Hence, it can be concluded that the intermolecular contribution can be neglected, and only the intramolecular H-bond dynamics as well as its coupling with the solvent has to be considered.



Fig. 2. ¹H NMR spectrum of PANO + 4-nitro-PANO (R = NO₂) dissolved in ACN- h_3 as the evidence of slow intermolecular H-bond proton exchange (0.3 M, *T* = 293 K).

The proton transfer from the donor (O1) to the acceptor (O3) has to be considered in this case. The driving force for PT is the electric field created by the electric dipoles of solvent molecules at the H-bond site [16]. Therefore, a crucial role of dielectric media in PT processes is stressed almost in all studies on this topic. The strength of the proton driving field depends on the ordering of individual dipoles of solvent molecules. The questions concerning the extent of this dipole ordering, like - is it either an overall or structuring effect that covers only a part of solvent molecules in the closest surrounding of H-bond complex, and the rate of solvent reorganization are still open. Not only dipoles of solvent molecules are important in PT processes. The concept of solvatomers [17-19] can be also considered explaining the changes in the proton position in the intramolecular H-bond and relating it to the solvation pattern around the oxygen atoms. According to this concept, a solution is disorganized, with one of the sites instantaneously solvated better than the other [18], leading to the presence of equilibrating solvatomers (isomers, stereoisomers, or

tautomers that differ in solvation) [19]. Thus, any changes in the dynamics of solvent molecules could then modify the rate and depth of PT in the solute molecules.

It is quite logical to expect that the ¹H chemical shift of the bridge proton can be used as the most effective diagnostic tool sensing the solvent properties via the H-bond dynamics. This is because the PT path and the motion of solvent molecules are coupled. Thus the rates of solvent molecular reorganization are very important for PT reactions. Therefore, the temperature dependences of ¹H NMR parameters (chemical shift and width) of –COOH proton in PANO in both isotopomers (ACN- h_3 and ACN- d_3) were studied very precisely covering the whole liquid phase from ACN melting to boiling points. The results obtained using the samples prepared under ambient conditions (see Experimental) are presented in Fig. 3.

No isotopic differences are seen on the dependences of chemical shift and signal width in the temperature range up to ~ 292 K (Fig. 3). The dependencies of chemical shift are linear, characterized by the same slope (0.0062 \pm 0.0001 ppm/deg) in both solvents. The picture is drastically changing at temperatures above 292 K. The changes in the ACN- h_3 solution look like a second-order liquid-liquid phase transition occurred. The linear dependence of chemical shift transforms to the more complex one, whereas no changes in temperature regime is seen in ACN- d_3 (Fig. 3a). The differences between ACN- h_3 and ACN- d_3 become more obvious looking at the dependences of signal width on temperature (Fig. 3b). These dependences remind those formerly observed in IR and Raman experiments on pure ACN- h_3 and ACN- d_3 together with isotopic and chemical equimolar mixtures, where this observation was called as an unresolved *casus* [6]. There was also claimed that a qualitative interpretation is possible, if it is accepted that the isotopic substitution can substantially modify the local structural organization of these molecular liquids.



Fig. 3. Temperature dependences of ¹H chemical shift (a) and signal width (b) of –COOH proton of PANO in solutions prepared under ambient conditions in ACN- h_3 and ACN- d_3 , respectively.

The results obtained in the present work using NMR spectroscopy reveal some new aspects of this problem in more details. Several overlapping factors that can cause the observed anomalies in ACN- h_3 and ACN- d_3 solutions can to be noted:

i) The presence of traces of water in the samples prepared under ambient and high-level conditions.

Water molecules are always present in solutions in certain amounts in the samples prepared under ambient conditions. Note, this level of sample preparation is often met in many works done using 'fast' methods of spectroscopy (FTIR, Raman). According to a wide spread opinion, the presence of water in micro-amounts can be neglected as the vibrational bands of water can be easily recognized, separated from others and analysed. Often this is true. Therefore FTIR spectroscopy was applied in the present work in order to check and to compare the water content in ACN- h_3 and ACN- d_3 . As it follows from the FTIR spectra (Fig. 4), the amount of water was practically the same as in ACN- h_3 as well as in ACN- d_3 .



Fig. 4. FTIR ATR spectra of ACN- h_3 (**III**) and ACN- d_3 (**II**) under ambient conditions. The spectra were recorded on BRUKER-ALPHA spectrometer.

The situation differs when NMR methods are used. Because NMR is 'slow' spectroscopy and the averaging of signals of nuclei involved in fast dynamic processes occurs, the NMR users always sought to minimize in their works the amount of water. It is hard to recognize, however, some micro traces of water have survival in the samples prepared under ambient

conditions and studied in the present work. The corresponding signals were detected in the ¹H NMR spectra at very large zooming of intensities (Fig. 5). It is worthy to note that ¹H NMR spectroscopy looks to be the unique method that reveals very fine differences in water structuring/aggregation in ACN- h_3 and ACN- d_3 solutions. These differences can be identified analyzing the signal shapes in the range of 2 - 6 ppm (Fig. 5) and some peaks can be attributed to water in various states of aggregation.



Fig. 5. The traces of water observed at 2 - 6 ppm in the ¹H NMR spectra of PANO in ACN- h_3 (**III**) and ACN- d_3 (**II**) solutions. The evolution of signal shapes in both solvents is shown separately in two inserts at increasing temperature (240, 273, 323 and 345 K).

The effect of high-level sample preparation is shown in Fig. 6. In order additionally to reduce the presence of water that may come to solutions together with PANO, despite it was dried under vacuum (see Experimental), its concentration was reduced to 0.03 M. The convergence of two regimes of H-bond dynamics in PANO in both solvents (ACN- h_3 and ACN- d_3) can be stated by reducing of the amount of water (Fig.6).



Fig. 6. The effect of high-level sample preparation on the temperature dependences of signal width of –COOH proton of PANO. The samples prepared under ambient conditions: 1, 2 – solutions of 0.3 M of PANO in ACN- d_3 (**II**) and ACN- h_3 (**III**), respectively; the samples prepared in the glovebox: 3 – 0.03 M of PANO in ACN- d_3 (**II**), 4 – in ACN- h_3 (**III**) kept over molecular sieves, 5 - in anhydrous ACN- h_3 (**I**) and no molecular sieves. More details are given in Experimental.

ii) Liquid-liquid equilibrium in ACN/water solutions.

It is well-known [20-22] that the aqueous ACN solution exhibits the second-order phase transition characterized by the phase diagram with the upper critical solution temperature (UCST) at ~ 272 K and at the concentration 0.36 - 0.38 mole fraction of ACN (Fig. 7a). The microscopic and

mesoscopic mixing scheme changes drastically, dependent on concentration and temperature, especially in the neighborhood of the critical point. The small-angle X-ray scattering experiments confirm that indeed the fluctuations of concentration became very large approaching to UCST [20] (see the dashed area in Fig. 7a.).



Fig. 7. The possible scenario of the evolution of phase diagram (T vs X_{ACN} (concentration in mole fraction)) of aqueous ACN- h_3 and ACN- d_3 solutions upon ionic and isotopic effects. The data taken from [21,22] were used illustrating the changes of phase diagrams $a \rightarrow b$ and $a \rightarrow c$. The critical regions of large fluctuations are shown by the dashed areas. More comments in text.

The UCST in ACN/water solution looks to be rather far away from ~ 292 K, i.e. the point where the onset of anomalies was observed in ¹H NMR spectra in the present work (Fig. 3). However, it is also known that even very small amount of ionic solute can drastically influent the phase equilibrium shifting the UCST to much higher temperatures [22,23].

iii) Effect of ionic solute.

Binary mixtures of water with added organic components like ACN or tetrahydrofuran (THF) are often used in modern bio- and nano-technological applications. Usually ACN and THF solutions in H₂O or D₂O are accepted to be homogeneous at room temperature for any molar ratio of the components. However, dissolved ions, even a miserly amount, can change their phase diagrams very significantly [22,23]. Namely, the phase separation temperature (or UCST) in ACN/water mixtures can be shifted upon dissolving of ions (K⁺, Cl⁻, KPS, etc.) from 272 K to 280 K or even to higher values, particularly, if water is present in small amount [22]. The ionic effect on the phase diagram (liquid - liquid coexistence curve) is shown in Fig. 7b. Furthermore, as it was noted in the studies of very strong H-bond between pyridine N-oxide (PyO) and HCl in ACN solution, the Hbond systems with PT can act as an ionic solute [24]. It was observed that very low solubility of the PyO.HCl co-crystal in ACN (ca. 0.1 M at the room temperature, i.e. even lower than PANO in the present case) can be improved by adding of some amount of H₂O or D₂O. However, a rather inhomogeneous composition of ACN/H2O/PyO/HCl was obtained in this case. The presence of micro inhomogeneities in the sample is not always noticeable visually. However, even a small perturbation of temperature renders the sample turbid, and consequently the phase separation is induced. The ionic structures PyO.H⁺...Cl⁻ that appear thanks to PT process are acting as ionic ingredients. It would be logically to assume, that PANO molecules could also play a role of ionic ingredients while the virtual ionic pairs appear during the fast intramolecular PT (Fig. 1). The time

scale of the oscillation of ionic forms in PT process in the range of $\leq 10^{-5} - 10^{-6}$ s, as it that follows from the ¹⁷O NMR spectrum (Fig. 1), should be noted particularly. This seems to be a very interesting parallel with the intramolecular charge transfer and fluorescence results obtained studying the solvation dynamics of dye molecules in ACN solutions [10]. There was deduced that the nanosecond-component in both ACN isotopomers were substantially different, however, no effect in ultrafast (fs and ps) solvation time scale.

iv) Deuterium isotope effects on phase separation in organic solute/water mixtures.

According to the FTIR data (Fig. 4), the amount of traces of water was practically the same in both solvents (ACN- h_3 and ACN- d_3). Therefore, the above factors (i - iii) solely cannot explain the differences in the observed isotopic effects (Fig. 3). However note, the deuteration of organic solute in aqueous solutions leads sometimes to rather unexpected phenomena. A very revealing example of such behavior is met in the case of THF/water solutions. The solutions of THF- h_8 in D₂O and H₂O possess the so-called closed-loop' phase diagram possessing the lower and the upper critical solution temperatures (LSCT and UCST; 336.9 K and 416.7 K in D₂O, respectively) [23]. It is very surprising, but the closed-loop phase diagram disappears in THF- d_8 aqueous solutions. THF- d_8 was found to be perfectly miscible with water, either H₂O or D₂O, for any molar ratios. The phase separation in these mixtures can be induced by dissolving of salts. Depending on the concentration of ions, the liquid - liquid phase separation can appear even at the room temperature. The play with solute deuteration can be continued - the miscibility gape appears again in the THF- h_4d_4 /water solutions, however, it is narrower than in the case of THF- h_8 [23].

Unfortunately, the complete phase diagram for the ACN- d_3 /water solutions, to the best of our knowledge, was not determined or published. Only the increase of UCST by + 0.6 K upon deuteration of ACN and about + 6 K upon replacement of H₂O by D₂O was reported [21]. This situation is symbolically pictured in Fig. 7c. The total effect of all of these contributions (i-iv) is

presented in Fig. 7d. The region of critical mixing/demixing regimes (the dashed area in Fig. 7d) can be pushed then to the conditions actual for the present work (~ 292 K, at the micro-amount of water, i.e. $X_{ACN} \rightarrow 1$). Until the precise phase diagrams for ACN- d_3 /ACN- h_3 /water/ions are not determined for a wide range of concentration, the drawing in Fig. 7d has to be treated as the hypothesis or as a directing-post for the future experiments. However, a such scenario is at a certain level supported by the NMR experiments carried out in this work (Fig. 5) as well as by the things NUS known for the related systems (refs 21-24).

Concluding remarks

The obtained results allow to conclude that the latter factor, viz. - the deuterium isotope effects on the phase separation in organic solute/water mixtures should be considered as the most crucial. It causes the observed differences in the properties of ACN- h_3 and ACN- d_3 , as solvents, called in the literature as anomalies or casus. The liquid-liquid phase separation in its physical matter is the second-order phase transition. Therefore, rigorously the casus with ACN- h_3 and ACN- d_3 can be explained constructing the proper second-order phase transition model/treatment, in which the vibrational contributions of different isotopes to the intermolecular interaction energies would be properly taken into account.

As ACN is widely used as a solvent or co-solvent in many kinetic and spectroscopic experiments, this is very revealing example illustrating how the traces of water, even in the microamount, can modify the properties of solvents and thus can distort the experimental outcomes.

¹H NMR spectroscopy is a very proper tool that can be effectively used sensing does the micro-structuring or phase separation occur in the chosen solvent at all. Very fine details of micro-heterogeneity, clustering or confinement of water molecules can be recognized applying this

method (Fig. 5). Then, looking ahead, this technique can be applied monitoring the liquid-liquid phase separation at the conditions where other experimental methods traditionally used determining the phase coexistence curves (light scattering, viscosity, refractive index, etc.) appear to be not capable.

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Graphic abstract



Highlights

Non-trivial effect of isotopomers of acetonitrile, as reaction media, on H-bond dynamics was deduced

Traces of water, even in the micro-amount, substantially modify the structuring of acetonitrile

Isotopic substitution $CH_3 \rightarrow CD_3$ influents the micro-structuring and local fluctuations in solvent

Structuring can distort the experimental outcomes of kinetics that occur in micro- to nanoseconds scales