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A New Structural Technique for Examining Ion-Neutral Association in Aqueous Solution

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Abstract

The method of intramolecular coordination number concentration invariance (ICNCI) is used on neutron diffraction with isotopic substitution (NDIS) measurements of aqueous solutions to separate the intra- and intermolecular contributions to the total intensities. Molecular dynamics simulations of corresponding systems are then used to interpret the ICNCI function. It is found that the ICNCI function (characterized by two concentration measurements) is sensitive specifically to intermolecular association and that the molecular dynamics can successfully replicate this function in the cases of the neutral species xylose and pyridine in aqueous solution. ICNCI functions can also be obtained by the addition of a cosolute (such as adding GdmCl or Gdm₂SO₄ to pyridine solutions). In that case it is found that molecular dynamics can replicate the ICNCI function for the addition of GdmCl to pyridine, but fails to successfully replicate the same function for the addition of Gdm₂SO₄. This result implies that the interaction of pyridine with guanidinium sulfate is over-estimated in MD these simulations, and is of significant importance to the use of molecular dynamics simulations to elucidate an atomic level understanding of the Hofmeister series.

Introduction

Key to obtaining an atomic level understanding of the Hofmeister series is acquiring the structural changes that such ions effect on the solutions. Obtaining insight into the structure of aqueous solutions is hampered by the fact that what is measured is rarely what is desired. The most frequently required structural insight into biochemical systems relates to their intermolecular associations. Here we describe the application of a new structural technique, internal coordination number concentration invariance (ICNCI), to a variety of solutions of both xylose and pyridine and show how this technique can yield useful structural information on the intermolecular associations in these solutions.

Direct structural techniques (e.g. neutron diffraction) are clearly better for examining the structure of condensed matter than the less direct inferences obtained from spectroscopic methods. Neutrons offers several advantages over x-rays in diffraction measurements, with

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the primary one being that they are scattered by the nuclei themselves, which are essentially point sources, while x-rays are scattered by the diffuse electron clouds. Another advantage is that hydrogen atoms are very visible in neutron diffraction while they are almost invisible to x-rays. Furthermore, hydrogen and deuterium are both readily available and clearly distinguishable in neutron diffraction experiments. Nonetheless, neutron diffraction from an aqueous solution, which involves correlations from every atom to every other atom, is typically so complicated as to defy easy interpretation. For example, even with a relatively simple solution like pyridine in water, there are five types of nuclei: the oxygen and the exchangeable hydrogens (Hex) of the water, and the non-exchangeable hydrogens (Hnon) and carbon and nitrogen atoms of the solute, producing 15 different pairwise correlation functions, so that the neutron diffraction pattern from the solution is a weighted sum of all 15 pairwise distribution functions. As a result, the interpretation of the diffraction pattern in terms of the individual atom-atom correlations presents a formidable challenge. Moreover, as the number of types of atoms in the sample increases, these correlations become progressively more difficult to disentangle.

Neutron diffraction with isotopic substitution (NDIS) was developed to simplify the interpretation of the structural data obtained from diffraction experiments.¹ This method involves performing paired experiments in which one atom type is replaced by an isotope of the same element with a different neutron scattering length, under the important assumption that the overall structure is not altered by the substitution. Subtracting the structure factors for the two experiments then eliminates all correlations except those involving the substituted atom.² In the pyridine example cited above, such a first-order difference experiment can be performed using H/D substitution on the Hnon atoms of the pyridine, reducing the 15 correlations in the total scattering measurement to just five: Hnon-C, Hnon-N, Hnon-Hex, Hnon-O and Hnon-Hnon. Such experiments have been effective in the study of the solution structure of many simple solutes such as rare gases³, mono-atomic ions^{4,5}, and approximately spherical molecular solutes⁶. In recent years, NDIS methods has been applied to much more complex molecular species including *tert*-butyl alcohol^{7,8}, ethanol, phenol, D-glucose⁹, amino acids^{10–12}, and polymer electrolytes.^{13,14} However, the interpretation of these experiments is impeded by the intramolecular correlations, which tend to produce very sharp and large correlations compared with the intermolecular (solute-water and solute-solute) correlations that are of primary interest. To circumvent this difficulty we developed the technique of internal coordination number concentration invariance (ICNCI).¹⁵ ICNCI uses the fact that the coordination numbers of the intramolecular correlations, particularly for rigid solutes such as pyridine, are relatively independent of concentration, while intermolecular correlations are strongly dependent on it. It is therefore possible to perform two NDIS measurements at different concentrations and numerically separate the components that vary with concentration from those that do not. Interpretation of this ICNCI function using information from molecular dynamics simulations of the same solution can lead to insight into the solvation structure of the species in solution. In this work we use the ICNCI technique on aqueous solutions of D-xylopyranose (doubly-substituted with deuterium at the non-exchangeable C5 hydrogen positions, Figure 1), and pyridine (H/D substituted on all the non-exchangeable hydrogens, Figure 1), and also on solutions of pyridine in GdmCl and Gdm₂SO₄.

Procedures

While the method of ICNCI is described in detail elsewhere,¹⁵ it is necessary to declare the functions measured in this paper. The total measured intensity for the sample ($F(Q)$) is given by

$$F(Q) = \sum_{\alpha} \sum_{\beta} c_{\alpha} c_{\beta} b_{\alpha} b_{\beta} (S_{\alpha\beta}(Q) - 1) \quad (1)$$

where c_{α} is the atomic concentration of species α , b_{α} is the coherent neutron scattering length, and the sums are over all the atomic species in solution. In this equation, $S_{\alpha\beta}(Q)$ is the partial structure factor for atoms α and β . The partial radial distribution function $g_{\alpha\beta}(r)$ is derived from $S_{\alpha\beta}(Q)$ by Fourier transformation.

While, in principle, it does not make any difference what the substituted nucleus is, we will first discuss the example of xylose. The aqueous xylose solution in this study contains 6 types of nuclei: Hex (exchangeable hydrogen atoms on water and xylose); Ow (water oxygen); C (carbon in xylose); Ox (oxygen in xylose); Hnon (the non-exchangeable hydrogen atoms of xylose, excluding the substituted nuclei); and H5 (the substituted nuclei, see below). Note that while each of the unlabeled non-exchangeable protons Hnon is in a unique stereochemical environment, they are considered to be effectively equivalent here. Thus, the $F(Q)$ of this solution is the sum of 21 weighted partial structure factors. Two $F(Q)$ measurements are then made on chemically identical solutions, the first containing xylose with the H5 positions containing natural abundance hydrogen, the second with these hydrogens substituted with deuterium. When the first order difference is applied to the $F(Q)$ s of these two solution, all of the correlations exactly cancel except those that involve structure factors containing the substituted nuclei H5. This difference reduces the number of summed correlations from 21 in $F(Q)$ to 6 in $\Delta S_{H5}^X(Q)$,

$$\Delta S_{H5}^X(Q) = F_{d5,d5-xylose}(Q) - F_{natural-xylose}(Q) \\ = A [S_{H5Hex}(Q) - 1] + B [S_{H5Ow}(Q) - 1] + C [S_{H5Ox}(Q) - 1] + D [S_{H5C}(Q) - 1] + E [S_{H5Hnon}(Q) - 1] + F [S_{H5H5}(Q) - 1] \quad (2)$$

The superscript X indicates that the function contains only correlations from the substituted nuclei H5 to all other nuclei in the system. The transform of this function gives the single atom radial distribution function $G_{H5}^X(r)$,

$$G_{H5}^X(r) = A g_{H5Hex}(r) + B g_{H5Ow}(r) + C g_{H5Ox}(r) + D g_{H5C}(r) + E g_{H5Hnon}(r) + F g_{H5H5}(r) - G \quad (3)$$

where $G = A + B + C + D + E + F$ and $g_{H5}^X(r)$ is the radial distribution function for atoms X around the substitution-labeled position $H5$, and $A-F$ are the neutron scattering prefactors for each atom type (which in each case is equal to $c_{H5} c_X \Delta b_H b_X$, where c_X is the atomic concentration of each atom, b_X is the coherent neutron scattering length of each atom type X , and $\Delta b_H = b_D - b_H$ (deuterium and protium, respectively)). In this study, two first order differences on xylose were obtained, the first at 2 molal and the second at 5 molal. The neutron scattering prefactors $A-F$ for first order differences at these concentrations are given in Table 1.

The method of ICNCI was then applied to these solutions. If the conformation of the sugar does not change significantly with concentration, then it can be shown¹⁵ that an appropriately scaled subtraction of these two data sets will yield a difference function that contains no correlations that are not sensitive to the concentration of the sugar. For reasons that are explained elsewhere,¹⁵ this scaled subtraction is slightly different for the real space data than for the reciprocal space data. For the real-space data this difference can be expressed as:

$$\Delta G_{H5}^X(r) = \frac{\rho_2}{c_{H5_2}} G_{H5}^X(r)_2 - \frac{\rho_1}{c_{H5_1}} G_{H5}^X(r)_1. \quad (4)$$

and for the Q space data it is expressed as:

$$\Delta \Delta S_{H5}^X(Q) = \frac{1}{c_{H5_2}} \Delta S_{H5}^X(Q)_2 - \frac{1}{c_{H5_1}} \Delta S_{H5}^X(Q)_1, \quad (5)$$

This technique may be applied equally well with the addition of a co-solute to the solution. For example, if a first order difference is measured with 3 *m* pyridine, and a second measured for 3 *m* pyridine in solution with 3 *m* GdmCl, application of both equations 5 and 6 will yield an ICNCI function that contains no intramolecular correlations. This ICNCI function then gives information on the difference in the solvation of pyridine in water and in 3 *m* GdmCl solution.

Experimental

Seven first-order difference experiments are conducted in the present study (summarized in table 2). These consisted of aqueous solutions of 2 and 5 *m* xylose (with H/D substitutions on both of the C5 hydrogen atoms); 1, 3 and 5 *m* pyridine (with H/D substitutions on all of the non-exchangeable hydrogen atoms); 3 *m* pyridine with 3 *m* GdmCl; and 3 *m* pyridine with 1.5 *m* Gdm₂SO₄.

Samples of D-xylose doubled-labeled with deuterium (>95% enrichment) at the H5 positions were purchased from Omicron, Inc., and natural abundance D-xylose was purchased from Sigma. Xylose solutions were prepared by placing about 1 g (carefully weighed) in a flask of known mass. About 3 ml of D₂O was then added and was mostly removed under vacuum. This process was repeated four times in total before the correct amount of D₂O was gravimetrically added to make the solution up to 5 molal (about 1.3 g). A 1 ml aliquot of this sample was then placed in the neutron cell (a null scattering Ti/Zr alloy) and diffraction measurements were carried out for about 4 hours. The sample was then transferred back to the flask of known mass, and the sample cell washed out with D₂O. Further D₂O was then gravimetrically added to the flask of known mass to dilute the sample to the desired concentration of 2 *m*. After thorough mixing, 1 ml of this solution was transferred to the neutron scattering cell and data were collected for about 4 hours. Solutions of pyridine/water and pyridine/solution were prepared by direct mixing of pyridine with the solution in question (total solution volume was typically ~2 ml). Solutions of guanidinium salts were prepared by the addition of D₂O to the salt (a known amount in a flask of known weight) to achieve approximately the correct concentration. The D₂O was removed under vacuum and more D₂O added. This procedure was repeated 4 more times and finally the correct amount of D₂O added to effect the correct concentration. These solutions were then used to prepare the Gdm salt-pyridine solution. All data were corrected for multiple scattering and absorption, and normalized versus a vanadium rod using standard procedures.^{14,16} All measurements were performed on the D4C diffractometer at the Institut Laue-Langevin (ILL, Grenoble, France).¹⁶

Molecular Dynamics (MD) Simulation Procedures

Neutral and periodic cubic systems were created at 2 and 5 molal concentrations containing a number of independent xylose and water molecules interacting according to the CSFF sugar force field^{17,18} and the modified TIP3P model^{19,20} for water. All simulations were performed with the CHARMM program^{21,22}, with chemical bonds to hydrogen atoms kept

fixed using SHAKE²³ and with a time step of 1 fs. The starting coordinates for the 2 *m* system were created by placing 33 randomly orientated xylose molecules (consisting of 22 β and 11 α anomers) in a 34 Å cube. The ratio of 2 β : 1 α is close to that of a D-xylose solution at anomeric equilibrium. These coordinates were superimposed on a box of 1296 water molecules, and solvent molecules that overlapped with the solutes were deleted, using an arbitrary separation cutoff, to produce the correct concentration (33 xylose molecules and 917 TIP3P water molecules, 1.999 *m*). Finally, the box length was rescaled to 32.0613 Å, which yielded the correct physical number density (0.1035 atoms Å⁻³). The 5 *m* solution, created in the same manner, contained 60 xylose molecules and 667 TIP3P water molecules, giving a concentration of 4.998 *m*. The box length was then rescaled to 30.9471 Å, which yielded the correct physical number density (0.1080 atoms Å⁻³). All van der Waals and electrostatic interactions were smoothly truncated on a neutral group basis using switching functions from 13 to 15 Å. Initial velocities were assigned from a Boltzmann distribution (300 K) followed by 10 ps of equilibration dynamics with velocities being reassigned every 0.2 ps. The simulation was then run as an NVE ensemble for 1.0 ns with no further velocity modification. The first 0.33 ns of the trajectory was used as equilibration, and the remaining 0.67 ns for analysis.

Similar procedures were used for the simulation of 1 and 5 *m* pyridine solutions, and for 3 *m* pyridine, (10 ns, 56 pyridines, 1036 waters, box size 33.6771 Å, number density 0.0975 atoms Å⁻³), 3 *m* pyridine/3 *m* GdmCl (10 ns, 36 pyridines and 36 GdmCl, 667 waters, box size, 30.6312 Å, number density 0.0972 atoms Å⁻³), and 3 *m* pyridine/1.5 *m* Gdm₂SO₄ solutions (50 ns, 114 pyridine, 57 Gdm₂SO₄, 2114 waters, box size 44.8489, number density 0.100).

Results and Discussion

To demonstrate the validity of this approach (even for a more conformationally flexible solute such as xylose), the ICNCI function was calculated from the molecular dynamics data. The functions $G_{H5}^X(r)$ at both concentrations (2 and 5 *m*) and the ICNCI function $\Delta G_{H5}^X(r)$ as calculated from the MD simulations are shown in Figure 2. The difference function $\Delta G_{H5}^X(r)$ shows no evidence of intermolecular correlations, suggesting the validity of the application of the technique of ICNCI to potentially more flexible solutes such as xylose. This result is not surprising given that molecular dynamics simulations of the similarly conformationally-flexible glucose molecule showed no detectable ring conformational changes over the concentration range 1–5 *m*.²⁴ The contrast (the sum of the scattering prefactors *A* through *F* (see Table 1)) in the 2 *m* NDIS experiment was 24 mb, while it was found that the contrast of the function $\Delta G_{H5}^X(r)$ was about 2 mb (estimated from the high *r* limit from Figure 2). This is near the limit of what can be experimentally measured, both due to the accuracy with which solutions of the correct atomic concentrations can be made, and due to the statistical counting error using current diffractometers. However the limitation of working so close to the statistical counting limit of the diffractometer is offset by the fact that the measurement is of direct relevance to the intermolecular association of the species in solution. It is topologically inevitable that as the concentration of the solute is increased, the solute-solute coordination number will increase, while the solute-solvent coordination number will decrease. Therefore, the function $\Delta G_{H5}^X(r)$ contains information about how the solute-solute and solute-solvent interactions vary with concentration. That is the function $\Delta G_{H5}^X(r)$ now contains exclusively structural data that is of relevance to the competition of the water-xylose/xylose-xylose interactions.

The MD simulations are invaluable for examining the constitution and general features of such functions. Since the pair correlation components of $\Delta G_{H5}^X(r)$ are additive, we can examine each component from the simulations separately in an ‘augmentation/exclusion’, or AE, plot (see Figure 3). Not surprisingly, it was found that water is excluded as the concentration of sugar increases. Therefore, the H5-Ow and H5-Hex components are both negatively weighted. Conversely, the coordination number of the sugar increases with concentration. However, the prefactor for H5-Hnon is negative, and consequentially the curves corresponding to this increase in sugar coordination number are positively weighted for the H5-C and H5-Ox correlations, but negatively weighted for the H5-Hnon correlation.

While the signal in $\Delta G_{H5}^X(r)$ is broad and featureless at higher r , the directly measurable function $\Delta \Delta S_{H5}^X(Q)$ (as predicted from MD, and directly related to $\Delta G_{H5}^X(r)$) shows a very characteristic signal at $Q < 2 \text{ \AA}^{-1}$. This is the key diagnostic feature of the experimental data. Principally for this reason, the comparison of the ICNCI functions is better performed in Q -space than r -space (Figures 3 and 4).

The raw scattering data from the experiments, corrected for multiple scattering and absorption, and normalized to a standard vanadium rod, produces the total scattering patterns ($F(Q)$ s) shown in Figure 4. The most obvious observation from these data is that the solutions that contain more hydrogen have a higher scattering level, and appear to be on a higher slope. The higher level is a consequence of the very high incoherent scattering cross section of hydrogen, while the slope is due to the inelastic recoil of the protium nucleus (the Placzek effect^{25,26}). For both the 2 and the 5 m solution the first order difference was obtained by the subtraction of the $F(Q)$ for the natural abundance xylose solution from the $F(Q)$ for the $d5,d5$ -substituted xylose solution. Both of these first order differences, $\Delta S_{H5}^X(Q)$, are shown in Figure 4. There are two conspicuous differences between these two $\Delta S_{H5}^X(Q)$. First, the oscillations in the higher concentration function are larger due to the higher contrast of this difference, and second, the higher concentration function has a greater slope. This second point is a combination of the fact that the substituted nucleus is hydrogen, which contains significant contributions from the incoherent scattering, and of the Placzek effect. While these artifacts may seem large, it should be born in mind that this effect yields an extremely broad feature (wavelengths $\sim 80 \text{ \AA}^{-1}$) and does not contribute to the higher frequency components that are of interest in this study (wavelengths $0\text{--}10 \text{ \AA}^{-1}$).

For the other ICNCI differences in this study, similar AE plots can be derived from the MD data (Figure 4). As expected, the AE plots reflect the geometry of the molecule on which the NDIS substitution has been performed (xylose or pyridine). Further the AE plots show clearly different structural responses to either the changing concentrations of solute or co-solute. In order to obtain an accurate ICNCI function, the force field in question must be able to reproduce the balance of water-solute and solute-solute interactions. For ICNCI 1, the force field used satisfactorily reproduces the balance of the water-xylose and xylose-xylose interactions. For ICNCI 2 (the balance of pyridine-water versus pyridine-pyridine) this balance is also good, although not as satisfactory as with xylose. For ICNCI 2 the AE plot reveals that the majority of this function is due to pyridine replacing water in the pyridine solvation shell at higher concentration. The form of this interaction has been shown to be mostly comprised of T-type interactions.^{15,27} For ICNCI 3, the molecular dynamics force field seems to reproduce the relative balance of the associations in the pyridine-pyridine and pyridine-(pyridine + GdmCl) solutions acceptably. This solution has been studied in significant detail, where it can be shown that the majority of this ICNCI function is due to the stacking of the guanidinium ion with the pyridine.²⁷ However for ICNCI 4, the correlation between the experiment and the molecular dynamics is poor. In this solution it

was found that there is strong association between the guanidinium and sulfate ions, leading to nanometer sized clusters with lifetimes of tens of nanoseconds, similar to those observed previously.^{25,28} The pyridine shows a strong association to these clusters. While multiple separate lines of evidence support the suggestion that the association between guanidinium and high charge density anions such as sulfate is stronger than lower charge density ions such as chloride,²⁸⁻³⁰ it seems reasonable to suggest that the molecular dynamics in this case is significantly over-estimating the level of association of the $\text{Gdm}^+\text{-SO}_4^{2-}$ ion pair, and the interaction of the pyridine with these clusters. A possible explanation for this may be that in MD simulations with non-polarizable force fields such as those used here, the effects of the electronic polarizability of the water on the effective charge of the ion are not taken into account.^{31,32}

Conclusions

We have shown that the functions derived from ICNCI are useful for studying both flexible solutes such as xylose and ones like pyridine, and can be used by either by varying the concentration of the substituted solute, or by adding a co-solute. We find that the ICNCI function is surprising sensitive to the solute in question, showing different responses to the variation of concentration in xylose and pyridine, and a difference in solvation of pyridine between the addition of GdmCl or Gdm_2SO_4 . These results suggest that the interaction of pyridine with the $\text{Gdm}^+\text{-SO}_4^{2-}$ clusters in these simulations is significantly overestimated. Previously it has been suggested that the level of this ion pairing is important for the position of the ions in the Hofmeister series, and is also important in the formation of the salt bridges that contribute to the stability of proteins. This study suggests that there are some significant limitations in this type of molecular dynamics in obtaining the correct level of ion pairing in these simulations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Left: β -D-xylopyranose in the 4C_1 conformation; right: pyridine. In both cases the substituted hydrogen atoms are shown in purple.

Figure 2.

The MD predictions for the function $G_{H5}^X(r)$ at xylose concentrations of 2 and 5 m (lower grey and black lines, respectively). The upper black line shows the function $\Delta G_{H5}^X(r)$ (translated for clarity by $0.08 \text{ barns atom}^{-1} \text{ str}^{-1}$), and upper grey line the same function scaled by a factor of 10 (prior to translation).

Figure 3.

Upper: the real-space Augmentation/Exclusion plots; lower: the reciprocal-space ICNCI functions (as derived from eq. 5. red = experiment, black = molecular dynamics). In both the upper and lower plots the black line is the MD prediction of the ICNCI function. The color schemes for the AE plots, ICNCI 1, blue = exchangeable hydrogen, red = oxygen on water, grey = non-exchangeable hydrogens on xylose (negative weighting prefactor), purple = oxygen on xylose, cyan = carbon on xylose. ICNCI 2 (performed in null water so there is no exchangeable hydrogen correlation), red = oxygen, grey = carbon, blue = nitrogen, green = non-exchangeable hydrogens. ICNCI 3 (defined by pyridine-pyridine/GdmCl), red = oxygen, grey = exchangeable hydrogens, purple = carbon on pyridine, brown = carbon on Gdm⁺, blue = nitrogen on Gdm⁺, green = chloride. ICNCI 4, as with ICNCI 3 except green = oxygen on sulfate. For both ICNCI 3 and 4 components that make very minor contributions to these functions have been omitted for clarity. Minor corrections were made to the experimental ICNCI 1 and 2 (see supplementary material). ICNCI 3 and 4 are the raw experimental functions.

Figure 4.

Top left: the $F(Q)$ s for 2 *m* xylose in D₂O (grey, natural xylose; black, *d5,d5* xylose); top right: the $F(Q)$ s for 5 *m* xylose in D₂O (grey, natural xylose; black, *d5,d5* xylose). Lower left: the first order difference functions ($\Delta S_{H5}^X(Q)$) for the previous two plots (grey, 2 *m* xylose; black, 5 *m* xylose). Lower right: the function $\Delta \Delta S_{H5}^X(Q)$ as calculated from MD (upper grey), and directly determined by experiment (grey). The black line shows the fit obtained by altering the weighted subtraction necessary to obtain the function $\Delta \Delta S_{H5}^X(Q)$ by 9%. This figure graphically shows the size of the function $\Delta \Delta S_{H5}^X(Q)$ versus the original $F(Q)$ s. For details of a specific correction applied to ICNCI 1 see supplementary material.

The neutron scattering prefactors for the first order differences of D-xylose solutions substituted with deuterium at the H5 nuclei for the 2 and 5 molal solutions in D₂O.

Table 1

Prefactor	Correlation	Value in mb	
		2 molal	5 molal
A	H ₅ H _{ex}	15.51	25.63
B	H ₅ O _w	6.29	9.45
C	H ₅ O _x	1.13	4.25
D	H ₅ C	1.30	4.87
E	H ₅ H _{non}	-0.47	-1.76
F	H ₅ H ₅	-0.58	-2.19
Total (G)		23.76	42.44

Table 2

The details of the solutions examined in this study and the ICNCI functions calculated from the experimental and molecular dynamics simulation data.

Solution/Concentration	Xylose 2m	xylose 5m	pyridine 1m	pyridine 5m	pyridine 3m	pyridine 3m	pyridine 3m
Substitution	H/D Both Hnon on C5		H/D All Hnon			H/D All Hnon	
Composition of solution	D ₂ O	D ₂ O	Null water (Average scattering length of water hydrogen = 0)				1.5 m Gdm ₂ SO ₄ D ₂ O
ICNCI function calculated	ICNCI 1		ICNCI 2		ICNCI 3		
					ICNCI 4		ICNCI 4