Final report for OTKA Grant No. 108721
Bakó Imre Hydrogen bonded networks in condensed phases

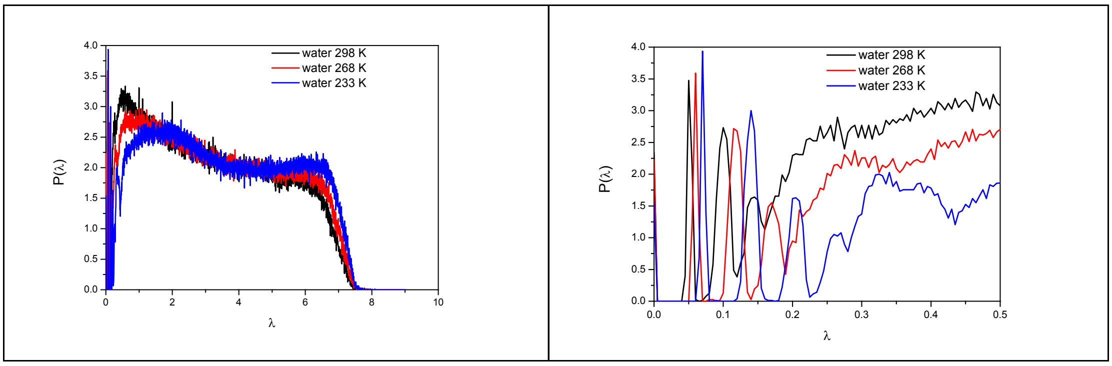
In the research proposal we planned to study the properties of three major types of systems: mixtures, hydrated crystals and proteins. During the course of the project we achieved significant results in all areas, and published all together **15** articles in peer reviewed journals and one manuscript has been submitted for publication. The outcome of our project is described in detail below, group according to the various subject areas studied by us.

Results concerning to the spectral properties of liquid water.

1. ***I. Bakó, Á. Bencsura, K. Hermanson, Sz. Bálint, T. Grósz, V. Chihaia, and J. Oláh*** **Hydrogen bond network topology in liquid water and methanol: a graph theory approach, PHYSICAL CHEMISTRY CHEMICAL PHYSICS 15 15163-15171 (2013)**
2. ***I.Bakó, I. Pethes, Sz. Pothoczki, L. Pusztaiˇ (J.Mol. Liq. 2018 Közlésre beküldve)*** ***T*****emperature dependent network stability in simple alcohols and pure water: the evolution of Laplace spectra**

We investigated and compared the topological properties of liquid water and methanol at various temperatures using concepts derived within the framework of graph and network theory (neighbour number and distribution, cycle size distribution, the distribution of local cyclic and local bonding coefficients, Laplacian spectra (distribution of eigenvalues of Laplace matrix) of the network, inverse participation ratio distribution of the eigenvalues and average localization distribution of a node) and compared them to small world and Erdős-Rényi random networks. Various characteristic properties (e.g. the local cyclic and bonding coefficients) of the network in liquid water could be imitated by small world and/or Erdős-Rényi networks, but the ring size distribution of water is unique and none of the studied graph models exhibited could imitate resembles it. We also demonstrate that the topological properties of the hydrogen bond network found in liquid water systematically change with the temperature (fig 1) and that increasing temperature leads to a broader ring size distribution. In our (2) work we showed how the size of the spectral gap in the Laplace matrix of H-bonded networks may be applied for characterising the stability of the network. This quantity does not depend on the applied water model (at least among the ones considered here). We introduced a new method for detecting the presence percolated network in these systems, too, via the investigation of the properties of the distribution of inverse participation ratio for eigenvalue ‘0’. We showed that the localisation of water molecules that belong to the network is significantly different from the ones that are not part of the percolated cluster

Fig 1. Laplace spectra of the H-bonded network in liquid water (SPC/E model at different temperatures). On the right side we showed the Laplacian spectra in a smaller range



Results concerning to the properties of liquid mixtures

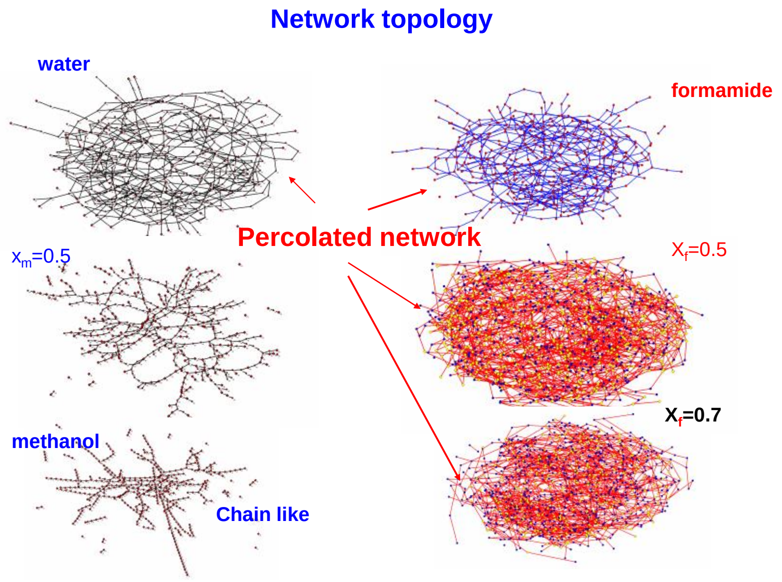
3. **I. Bakó, J. Oláh, A. Lábas, Sz. Bálint, L. Pusztai, M. Claire Bellissent Funel: Water-Formamide Mixtures: Topology of the Hydrogen-Bonded Network, J. Mol. Liq.228 25, (2017)**

4. **I. Bakó, L. Teimleitner, L. Pusztai: Decreasing temperature enhances the formation of sixfold hydrogen bonded rings in water-rich water-methanol mixtures, SCIENTIFIC REPORTS, 7, 1073, (2017).**

We have studied the structure of water-formamide mixtures using neutron-diffraction and molecular dynamics simulations. At all studied formamide concentrations we found a very good agreement between measured total radial distribution functions and those obtained from molecular dynamics simulations.. In water-formamide mixtures the average hydrogen bonded neighbour number of molecules (water, formamide) and the distribution of H-bonded neighbour does not change significantly as a function of formamide mole fraction. In these mixtures the molecules form percolated network in all concentration. On the basis of the topological analysis reveals, that the composition of cyclic entities in these system are very close to ideal in contrast to the behaviour detected in methanol-water mixture, thus we find a microscopic homogenity in this system.

The evolution of the structure of liquid water-methanol mixtures (where we have already detected a structural microheterogenity concerning to the cyclic structure at room temperature) as a function of temperature has been studied by molecular dynamics simulations, with a focus on hydrogen bonding and existence of ring structure. The number of recognizable hydrogen bonded ring structures in some cases doubles while lowering the temperature from 298 to 213 K; the number of sixfold rings increases most significantly. An evolution towards the structure of hexagonal ice, that contains only sixfold hydrogen bonded rings, has thus been detected on cooling water-methanol mixtures. A pictorial representation of H-bonded network in water-methanol and water-formamide system is presented in Fig 2.

Fig 2. Representation of network topology in water-metahnol and water formamide mixture (bond: H-bond)



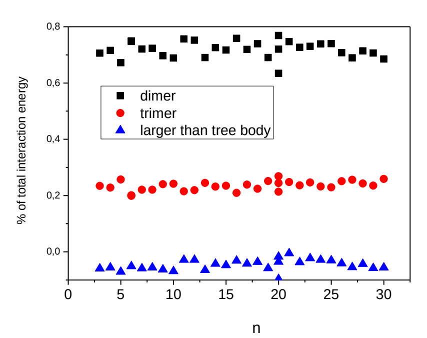
Results concerning the change of electronic properties of water in different environments.

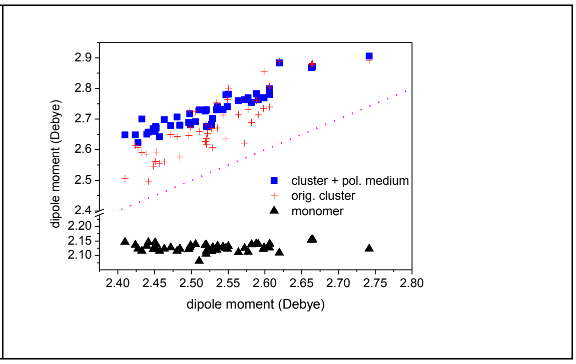
5. P. D. Mitev, I.Bakó, A. Eriksson and K. Hermansson
Large polarization but small electron transfer for water around Al^{3+} in a highly hydrated crystal, Phys.Chem. Chem. Phys. 16 : 9351-9363 (2014)
6. I. ***Bako ,I. Mayer***
On Dipole Moments and Hydrogen Bond Identification in Water Clusters
J. Phys. A 120. 4408-4417. (2016)
7. I.Bako I. Mayer
Hierarchy of the Collective Effects in Water Clusters
J. Phys. A 120. 631-638. (2016)
8. I.Mayer I Bako
Many-Body Energy Decomposition with Basis Set Superposition Error Corrections
J. Chem. Theo.Comput.13. 1883-1886. (2017)
Lectures:
Analysis of Hydrogen bond networks in water cluster (2-30) and liquid
CESTC 2014, Central European Symposium on Theoretical Chemistry
21-25 September 2014 Nagybörzsöny, Hungary
EMLG2014 Molecular Liquids and Soft Matter: from Fundamentals to Applications 7-12 September 2014 University Roma Tre Aula Magna del Rettorato
EMLG2016 – 11-16 September 2016, Crete – Greece" On Dipole Moments and Hydrogen Bond Identification in Water Clusters"
WATOC 2017 aug 27-1 Sept Muchen. Cooperative effects in water cluster

In this (5) paper we calculated the unique molecular electronic properties for highly hydrated crystals using DFT technique.. Electronic properties of nine structurally different water molecules in the $Al(NO_3)_3x9H_2O$ crystal have been calculated from DFT calculations.. We find very large Wannier dipole moments for H_2O molecules surrounding the cations: 4.0–4.3 D (compared to our calculated values of 3.1 D in liquid water and 1.83 D in the gas phase). These are induced by the ions and the H-bonds, while other water interactions and the relaxation of the internal water geometry in fact decrease the dipole moments. We find a good correlation between the water dipole moment and the O….O distances, and an even better (non-linear) correlation with the average electric field over the molecule.

The cooperativity of hydrogen bonds means that local hydrogen bond strengths and other electronic properties of the different water molecules are influenced by the neighbouring water molecules. One of the aims of this work was to better understand the origin and the size of these collective effects. We presented the values of dipole moments of individual water molecules as well as the results of the intra-and intermolecular bond order calculations indicating the big importance of collective electrostatic effects caused by the non-immediate environment in liquid water models (6, Fig2b) We discussed too how these collective effects build up as consequences of the electrostatic and quantum chemical interactions in water clusters. Additionally, we characterized how several local properties of a water molecule (dipole moment, relaxation energy) depend on the H-bonding environment and on the cluster size (7,8) It has been shown using energy partition method that the local H-bond strength depends on the H-bonding state of donor and acceptor molecules. Additionally we discussed the size of two, three body and relaxation energy terms using the Valiron Mayer counterpoise scheme (8) (Fig 2a)

Fig 2a The two ,three and many body contribution to the total interaction energy
Fig 2b. The dipole moment of water molecule in the different subsystems of water clusters.





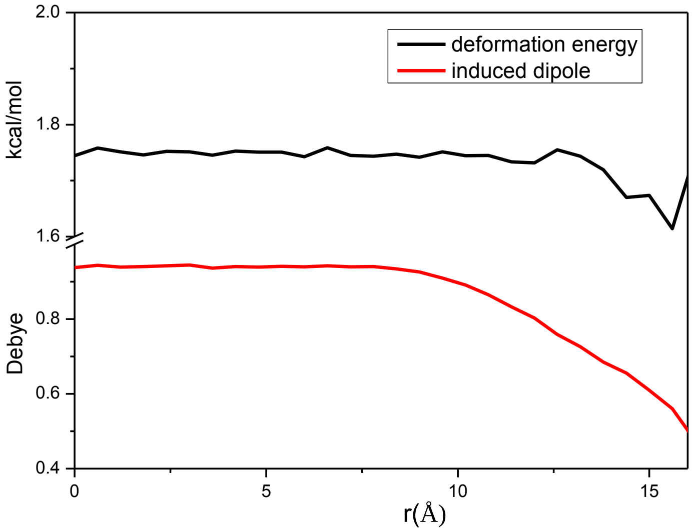
Results concerning to the H-bonded network structure on the interface

9. TC. ***Zhou, A. McCue, Y. Ghadar,I. Bakó,AE Clark***
Structural and Dynamic Heterogeneity of Capillary Wave Fronts at Aqueous Interfaces
J.Phys.Chem B 121. 9052-9062. (2017)
10. Anikó Lábas, Imre Bakó, Julianna Oláh
Hydration sphere structure of proteins: A theoretical study
J,Mol.Liq. 238. 462-469. (2017)

We studied the water network around insulin (10) in aqueous NaCl solutions using molecular dynamics simulations and statistical analysis of the topological properties (hydrogen bond neighbour number and the interaction energy between hydrogen bonded water molecules) of the water network. Water molecules in the first layer form significantly less, but stronger hydrogen bonds with each other than in the bulk phase and these molecule form a percolated network around protein surface. . Furthermore, water molecules over the hydrophilic and hydrophobic surface of the protein possess slightly different H-bonding properties, supporting the hypothesis of structural and dynamical heterogeneity of the water molecules over protein surface. Our data suggest the peculiar role of the second hydration shell.

Using a unique combination (9) of the slab-layering analyses and identification of truly interfacial molecules, this work examines water:vapor and water:n-hexane interfaces, specifically the structural and dynamic perturbations of the interfacial water molecules at different locations within the surface capillary waves. From both the structural and dynamic properties analyzed, it is found that these interfacial water molecules dominate the perturbations within the interfacial region, which can extend deep into the water phase relative to the Gibbs dividing surface. Heterogeneity of the interfacial water molecules at the capillary wave front is established beyond the typical metrics of the dipole orientation but also the structural and dynamic behavior of hydrogen bonds and their networks. In this paper we showed that the average H-bonded number in the same layer and different layers change very similarly in the case of rigid,nonpolarisable and flexible, polarizable (AMOBA) water models. In the first layer the average H-bond number is significantly smaller than in the second and third ones (the results for the third layer practically equal to the data for bulk water.). On the other hand the average bond energy for the H-bond is more negative (the bond is stronger) in the first layer in the TIP3P/Ew and more positive (the bond is weaker) in the first layer in the AMOBA model Additionally we showed than in the case of polarizable water model the induced dipole moment and deformation energy is smaller in the first layer than in the bulk. (fig3.)

Fig 3. The average dipole moment and averaged deformation energy of water molecule as a function of z



Results concerning to the local cooperativity in liquid water

11. ***I.Bakó A. Lábas, K, Hermanssoni,J. Oláh***

How can we detect hydrogen bond local cooperativity in liquid water: A simulation study

J. Mol Liq.. 140-146. (2017)

In this (11) paper we applied a method to the study the cooperative properties of the H-bond networks in liquid water which is widely used in network science for characterizing the mixing properties of real networks (social, technological and biological networks). Analysis of the cluster size distribution of the populations of water molecules with 3 and 4 H-bonds show that at 250 K water molecules with 4 H-bonds form an almost percolated network, however, the structure of the population of water molecules with 3 H-bonds is best described as a branched chain network at all temperatures.

Our results also indicate that at low temperatures water molecules with four H-bonds are likely to form H-bonds with each other, supporting the presence of low density patches. Furthermore, the Pearson's coefficient (global descriptor of local cooperativity) of the studied networks suggests that at normal density the H-bonded network in liquid water can be described by an uncorrelated network.

Results concerning enzymes

12. ***A. Lábas,B. Krámos,I. Bakó J.Oláh***

Accurate modeling of cation–π interactions in enzymes: a case study on the CDPCho:phosphocholine cytidylyltransferase complex

Structural Chemistry 26. 1411-1423. (2015)

13. B. Krámos, J.Olah he mechanism of human aromatase (CYP 19A1) revisited: DFT and QM/MM calculations support a compound I-mediated pathway for the aromatization process

Structural Chemistry 26 , 279-300 (2015)

14. A. Lábas, B. Krámos, J. Oláh

Combined Docking and Quantum Chemical Study on CYP-Mediated Metabolism of Estrogens in Man

Chem. Res. Toxicol., 30, 583−594 (2017)

Lectures

Application of hybrid quantum mechanics molecular mechanics (QM/MM calculations
B. Krámos, A. Lábas, J. Oláh, presented at:*
CESTC 2014, Central European Symposium on Theoretical Chemistry
21-25 September 2014 Nagybörzsöny, Hungary
Determination of proton and electron affinity of ligated heme iron centers in different enzyme families by QM/MM calculations
A. Lábas, B. Krámos, T. Szilvási, J. Oláh presented at:
CESTC 2014, Central European Symposium on Theoretical Chemistry
21-25 September 2014 Nagybörzsöny, Hungary

In our work (12) we propose a methodology for the accurate modelling of cation–p interactions in proteins using QM/MM calculations. Based on ideas taken from the studies of liquid water we also developed a methodology for computing the many-body interaction energy terms and tested their effects on the accuracy of the binding energy. The calculated interaction energies were only slightly influenced by electrostatic embedding of the point charges in the QM/MM calculations and by QM/MM geometry optimization. The calculated molecular mechanics interaction energies were off by 50 % for cation–p interactions. Instead, we suggest the calibration of force fields based on fragment based QM calculations on geometries obtained from MD simulations to yield reliable binding energies at reduced computational cost.

In (13) and (14) we studied estrogen biosynthesis and metabolism by P450 enzymes. In (13) we focused on the last step of estrogen biosynthesis, the aromatization of ring A of androstenedione or testosterone. We showed that human aromatase can efficiently catalyse the aromatization pro- cess via a compound I (or compound II)-mediated pathway. The nature of the oxidant is very sensitive to the polarizing environment of the enzyme, as the oxidant has a compound I nature in the gas phase calculations, which is modulated by the enzyme environment to become a mixed compound I and compound II character. The electronic structure of the obtained QM-only and QM/MM stationary points is thoroughly

In (14) we studied the structure of human estrogen metabolizing P450 enzymes (CYP1A1, CYP1A2, CYP1B1, and CYP3A4) in complex with estrone using docking and investigated the susceptibility of estrone, equilin, and equilenin (which only differ in the unsaturation of ring B) to undergo 2- and 4-hydroxylation using several models of P450 enzymes (Compound I, methoxy, and phenoxy radical). We found that even the simplest models could account for the experimental difference between the 2- and 4- hydroxylation pathways and thus might be used for fast screening purposes. We also show that reactivity indices, specifically in this case the radical and nucleophilic condensed Fukui functions, also correctly predict the likeliness of estrogen derivatives to undergo 2- or 4-hydroxylation.

1.

Results concerning to additional problem with proper acknowledgement.

a. Concentrated salt solution

15. T.Radnai, Sz. Bálint, I. Bakó, T. Megyes, T. Grósz, A. Pallagi, G. Peintler, I. Pálinkó, and P. Sipos The Structure of Hyperalkaline Aqueous Solutions Containing High Concentrations of Gallium - a Solution X-ray Diffraction and Computational Study Phys.Chem.Chem. Phys. 16 4023-4032, (2014)

Highly concentrated alkaline NaOH/Ga(OH)3 (11) solutions with 1.18 M Ga(III) 2.32 M and 2.4 M NaOH 4.9 M have been prepared and investigated by solution X-ray diffraction and also by ab initio quantum chemical calculations. The data obtained are consistent with the presence of only one predominant Ga(III)-bearing species in these solutions, that is the tetrahedral hydroxo complex Ga(OH)4– Moreover, higher mononuclear stepwise hydroxo complexes, like Ga(OH)63–, that have been claimed to exist by others in the literature, was not possible to experimentally detect in these solutions with any of the spectroscopic techniques used.

b. Determination in experimental accuracy in Isotopic substitution method

16. I. Bakó, G. Pálinkás, T. Grósz, Sz.s Bálint, G. Tóth and T. Radnai A new approach to the determination of the uncertainty in neutron diffraction experiments with isotopic substitution method J.Mol.Liquids ,198,5, (2014)

In this article, we suggest a method for the determination of the optimal set of H/D compositions with or without taking into account the experimental error. For the case of water, our investigations show that the selection of the isotope concentrations and the distribution of measurement time among the various samples have critical role if one wants to utilize the limited neutron beam time efficiently. On water and methanol as examples, we investigated the propagation of random errors to the partial structure factors using partial pair-correlation functions from molecular dynamics simulation.