

Propositions of PhD thesis

**BEHAVIOR OF PAMAM DENDRIMERS IN AQUEOUS
SOLUTION AND THEIR INTERACTION WITH SMALL
MOLECULES**

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I. INTRODUCTION AND THE AIM OF THE WORK

Dendrimers are artificial macromolecules with regular and highly branched structure. Poly(amidoamine) (PAMAM) dendrimers consist of ethylene-diamine and propionyl units, monomers build generations, forming nanosized, quite spherical macromolecules. There are tertiary amino groups in the branching points, peptide bonds and terminal (primary) amino groups on the branches (Figure 1). Through the protonation of tertiary and primary amines the molecule can gain even more than hundred positive charges. PAMAM dendrimers are hydrophilic, dissolve in water very well. Their behavior in solution, interaction with small molecules, as well as the effect of pH on their structure is very important from a utilization point of view.

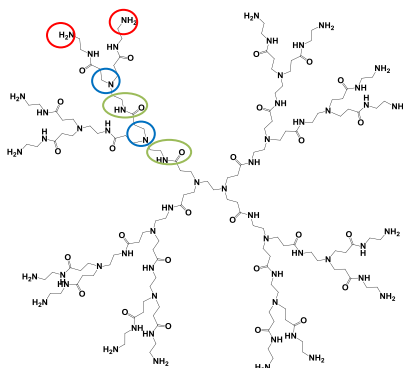


Figure 1. Structure and function groups of a generation 2 (G2) PAMAM dendrimer

Mainly neutron scattering techniques were used to get experimental data up to the present, and models were constructed with molecular dynamics calculations about the structure of PAMAM dendrimers in solution, and their interaction with the medium. However, the models and the experimental results showed differences about the pH-depending change of the size and inner structure of the molecules as well as the size of the cavities inside.

The importance of dendrimers in drug research is significant, as interacting with drug molecules they can get a role in the chemotherapeutic treatment of cancer as drug-delivery agents. The drug molecules can be covalently bound to the terminal groups, or they can be encapsulated in the supposed nano-size cavities (e.g. through hydrophobic interaction).

Due to the polyelectrolyte character of PAMAM dendrimers their interaction with ions is an important and interesting question. According to molecular dynamic simulations counter-ions compensate the charge of the dendrimer and shrink the structure. The behavior of the charged macromolecule in the presence of counter-ions cannot be described with the known formulas because of the numerous charges inside. The produced PAMAM dendrimers are often investigated in phosphate buffer, and also from therapeutic point of view, it is important to characterize the interaction of the macromolecules with phosphate ions.

PAMAM dendrimers have been used as templates for nanoparticles since their discovery, as they are able to stabilize metal nanoparticles making them water-soluble. Gold nanoparticles (AuNPs) are lately widely investigated and used because of their numerous advantages: with dendrimers they can serve as catalysts, X-ray and CT contrast agents, platform for cancer-cell targeting and imaging, nonviral vectors for gene delivery. The stabilization of gold nanoparticles with dendrimers can occur by encapsulation or steric stabilization. Generation 5 (G5) PAMAM dendrimers are appropriate templates for gold nanoparticles, but the way of stabilization is not clear.

It is important to know the structure in solution, the equilibrium processes and dynamics of polyelectrolytes like poly(amidoamine) dendrimers, thus the aim our work was to investigate the behavior of G5 PAMAM dendrimers in solution, and their interaction with the solvent (H_2O), small ions (H_3O^+ , Au^{III} , PO_4^{3-}), molecules (doxorubicin) and colloids (AuNPs of different size). From the results we draw conclusions about the possible applications.

II. EXPERIMENTAL METHODS

The nuclear magnetic resonance (NMR) characterization of G5 PAMAM dendrimers with NH₂ terminal group (G5.NH₂, Dendritech) and the investigation of its interaction with small molecules were carried out using a Bruker Avance DRX 400 NMR spectrometer. Spectra were evaluated with Mestrec and MestreNova 8.1© software. For the assignment of ¹H signals and the determination of the spatial structure ¹H, ¹³C, COSY (*C*orrelation *S*pectroscopy), NOESY (*N*uclear *O*verhauser *E*ffect *S*pectroscopy), ¹³C és ¹⁵N HMBC (*H*eteronuclear *M*ultiple *B*ond *C*orrelation) 1D and 2D spectra were recorded about the macromolecule dissolved in D₂O (Sigma Aldrich). The protonation of the dendrimer molecules was followed by ¹H NMR titration, the pH was set using DCl and NaOD solutions.

To get more information about the inner structure of G5.NH₂ molecules and their interaction with water, we prepared a dendrimer gel by adding water to solid, dried dendrimer crystals in four steps (1000-4000 water molecules/dendrimer). The pore size of this gel like material was determined by NMR cryoporometry. The gel was cooled in plastic NMR tube with minimum temperature of 239 K, an Eurotherm unit was used for stabilizing or regulating the temperature with liquid nitrogen or air flow through a Bruker BSCU 05 cooling unit. Increasing the temperature we recorded the ¹H NMR spectra of the liquid phase of the sample in every 0.5 K steps. The pore size can be determined from the melting/freezing point depression according to the modified Gibbs-Thomson equation (1):

$$\Delta T_{m/f} = T_{m/f} - T_0 = -\frac{nK_c}{r} \quad (1)$$

where $\Delta T_{m/f}$ is the melting/freezing point depression expressed as a difference between the bulk (T_0) and confined liquid ($T_{m/f}$) phase transition. K_c is the cryoporometric constant, n is a geometric factor and r is the pore size.

The interaction of G5.NH₂ dendrimers with phosphate ions was characterized by ¹H and ³¹P spectra at different pH values and phosphate

concentrations. The ratio of Na_2HPO_4 and $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ was changed to reach the desired pH. T_1 relaxation, NOESY and DOSY (Diffusion Ordered Spectroscopy) NMR experiments were carried out.

Dendrimer protonation was investigated with pH-potentiometry as well, in the presence and absence of phosphate ions ($I = 0,2 \text{ M KCl}$, $T = 298 \text{ K}$). The protonation constants of the dendrimer, the number of protonated groups and the composition of the new particle with phosphate were determined with HYPERUAD software.

The interaction of doxorubicin, as a chemotherapeutic drug, was studied with functionalized G5 PAMAM dendrimers: acetylated (G5.NHAc), hydroxylated (G5.GlyOH), and carboxylated (G5.SAH). For the possibility of the interaction aqueous solution of DOX and G5.NH₂ was prepared and neutralized with triethylamine. Using a longer sample preparation, DOX·HCl, dissolved in methanol, was added to the aqueous solution of the three different dendrimers. After mixing and separation the dendrimer-DOX complex was lyophilized. Redissolved in D₂O, ¹H, DOSY and NOESY spectra were recorded.

During the synthesis of dendrimer stabilized gold nanoparticle, HAuCl₄ solution was added to the dendrimer solution. ¹H and DOSY NMR experiments were carried out about the dendrimer filled with Au^{III}. Au^{III} was reduced with NaBH₄. After ¹H and DOSY measurements, the average diffusion constants were used to calculate the size of the hybrid nanoparticle with the Einstein-Stokes equation:

$$R_H = \frac{k_B T}{6\pi\eta D} \quad (2)$$

R_H is for the hydrodynamic radius, k_B is the Boltzmann-constant, T is for the temperature, η is the viscosity of the medium and D is the diffusion constant of the particle.

III. NEW SCIENTIFIC ACHIEVEMENTS

1. Characterization of G5.NH₂ dendrimer, the interaction with the solvent and its ions

1.1. Assignment of the ¹H NMR signals of G5.NH₂ dendrimer:

We have given the right ¹H NMR assignment of the G5.NH₂ dendrimer (Figure 2), which is often inaccurate in the literature, and performed a comprehensive NMR characterization about the macromolecule.

CH₂ groups in one dendron of the dendrimer, ignoring the branching, were numbered from 1-24 (Figure 3). Six types of CH₂ groups were differentiated according to the chemical environment, signed with different colors. We used the outer six CH₂ groups for the assignment.

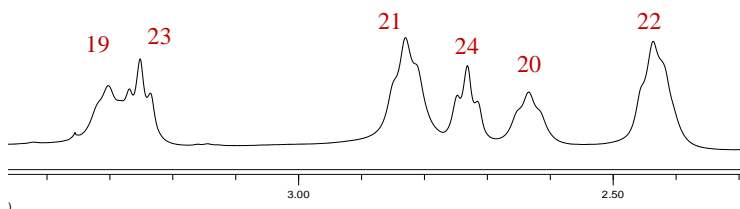


Figure 2. ¹H NMR spectrum of the G5.NH₂ dendrimer and the assignment of the signals (10 mg/g dendrimer in D₂O, pH =10.5, T = 298 K).

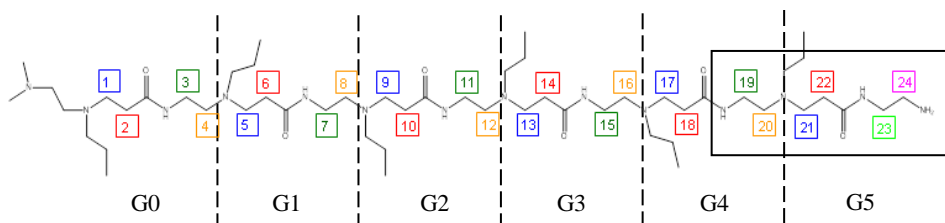


Figure 3. Numbering of CH₂ groups in G5.NH₂ dendrimer.

To assign the ¹H NMR spectrum (Figure 2), COSY, ¹³C HMBC and HSQC spectra were recorded. The NOESY spectrum showed dipolar

coupling between the protons near the tertiary amines in the branching points. We assigned the signals of the three different types of nitrogens in the dendrimer in the ^{15}N HMBC spectrum as well.

1.2. Interaction of G5.NH₂ dendrimer with water molecules, characterization of pores in dendrimer gel:

We have determined the pore size distribution of the pores in the G5.NH₂ dendrimer gel (Figure 4) using NMR cryoporometry. We have pointed out that the pores, with diameters of 3.6 and 5.2 nm, are formed by at least two dendrimer molecules. We have demonstrated that the diffusion of water molecules is restricted in the gel, and that the pores are connected, and their wall is penetrable for water.

When 1000 moles water molecules are present two pores appear with 1.8 and 2.6 nm radii supposing spherical pore shape (Figure 4). When the number of the water molecules increases to 2000 and 3000 per dendrimer, only the pore radius of 2.7 nm forms. In the case of the addition of 4000 water molecules the presence of a continuous water layer is remarkable. The result is in good accordance with our previously defined hydration number of about 3700 depending on the model.

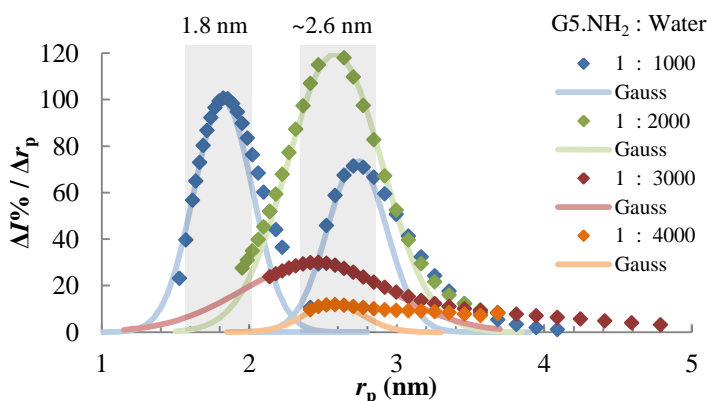


Figure 4. Pore size distribution in G5.NH₂ dendrimer gel.

Considering the size of the hydrated G5.NH₂ (~6.1 nm) we determined that the water droplets occur between the dendrimer molecules.

The diffusion time dependence of the diffusion rate was linear. The diffusion rate of water in the gels is slower than that of the free water and independent of the diffusion time.

1.3. pH dependent behavior of G5.NH₂ dendrimer, interaction with oxonium ions:

We have determined the protonation constants for the tertiary, $N_{(T)}$ and primary, $N_{(P)}$ amino groups of the G5.NH₂ dendrimer with two different methods. Using NMR titration we have proved the group constants determined by pH-potentiometry and separated the tertiary amino groups being in different chemical environment.

pH potentiometric titration of the dendrimer resulted in $pK_{N(T)} = 5,7(2)$ for tertiary amines, and $pK_{N(P)} = 8,9(2)$ for primary amino groups. The number of the protonating groups is 119 $N_{(T)}$ and 123 $N_{(P)}$, thus we have proved that the dendrimer structure practically corresponds to the structure given in the synthesis (126 $N_{(T)}$ and 128 $N_{(P)}$ in the case of completely correct structure). NMR titration was also carried out in the pH range 2-12.6. We have demonstrated that the protonation of $N_{(P)}$ occurs in the pH range ~7.5-10.5, while in the case of $N_{(T)}$ from pH ~4 to 8.5. We have calculated the protonation constants from the pH-dependent chemical shift change of the proton signals. In the case of tertiary amines we have showed that one part of tertiary amino groups binds protons weaker ($pK_{N(T)} = 5,76$), and the other part stronger ($pK_{N(T)} = 5,96$), according to the duplicated peaks. Although the experimental conditions were not exactly the same in the two methods, NMR titration makes the differentiation of the protonation constant possible, even in this case of numerous protonating groups.

The ¹H NMR spectra series from the NMR titration is essential in the NMR investigation of pH dependent reactions of G5.NH₂. The change of the ¹H NMR spectrum of the dendrimer with pH is often ignored in the literature.

2. Interaction of G5.NH₂ dendrimers with ions, small molecules

2.1. Incorporation of phosphate ions:

According to manifold NMR investigations we have determined that the phosphate buffer ($H_2PO_4^-/HPO_4^{2-}$), regularly used in structure determinations in solution and biological measurements, shows specific interaction with the G5.NH₂ dendrimer. The degree and nature of the interaction depends on the pH and the concentration circumstances. In the case of $pH < 6$ and $pH > 8$ phosphate ions form ionpairs with the terminal groups of the dendrimer, while between $pH = 6-8$ they are probably bound inside the macromolecule in $N_{(T)}H_2PO_4$ form.

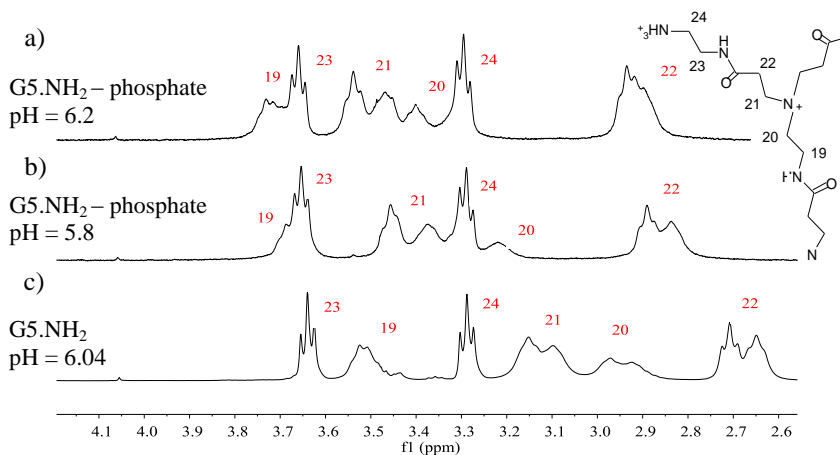


Figure 5. ¹H NMR spectrum of G5.NH₂ in the presence of phosphate ions (a és b) and without them (c) (10 mg/g dendrimer in D₂O).

The chemical shifts of the ¹H NMR signals of the protons around the tertiary amines (19-22) and the degree of peak duplication increase as an effect of phosphate ions (Figure 5). During the protonation of the tertiary amino groups, the protons of the outer fifth generation (no. 19-22) and that of the inner generations (no. 1-18) behave differently. On the basis of this experience we divided the structure of the dendrimer into three

regions. Primary amino groups and the near-by protons 23-24 form the outer region. Protons in the transition region (19-22 protons of the fifth generation) give peaks at higher chemical shifts in the ^1H NMR spectrum, which means less shielding of these protons. Their T_1 relaxation time is shorter ($T_1 = 0.33\text{-}0.4$ s), due to the smaller correlation time. The faster movement results in better resolution of the signals. Protons of the inner region (1-18 protons of G0-4) appear at smaller chemical shifts, and their T_1 relaxation is slower ($T_1 = 0.39\text{-}0.43$ s) in the protonation pH region than that of the protons in the transition zone. Since they can be found inside the macromolecule, the movement of these CH_2 groups is restricted thus the rotation correlation time is higher resulting in worse resolution.

The basicity of the amino groups increases in the presence of phosphate ions. We have determined the group constants of the tertiary and primary amino groups in the presence of phosphate ions using NMR titration: according to the duplicated peaks $\text{p}K_{\text{N(T)}} \approx 6.75$ and 6.5 (from the chemical shifts of the protons in the inner and transition region), while $\text{p}K_{\text{N(P)}} = 9.7$. These constant values are higher than that of the dendrimer without phosphate, meaning that the amino groups of the dendrimer bind the protons stronger in the presence of phosphate ions.

We have determined that the phosphate ions form one dynamic unit with the dendrimer in the whole pH range. The diffusion rate of the phosphate ions is lower than that of the free ions in the whole pH range, since a part of the phosphate ions move together with G5.NH_2 .

We have demonstrated that in the pH region 6-8 the diffusion constant of G5.NH_2 shows a maximum, the hydrodynamic size of the macromolecule decreases. In our explanation, tertiary amino groups start to protonate at pH less than 8, their positive charges are screened by $\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}$ -ions reducing the repulsion of protonated groups (Figure 6). Phosphate ions relax faster in this pH region resulting in increasing linewidth in the ^{31}P spectra. Phosphate ions can be found inside the dendrimer resulting in higher rotation-correlation time. With increasing phosphate concentration the size of the macromolecule gets smaller. According to our calculations as many as 145 HPO_4^{2-} and H_2PO_4^- ions can be built into the dendrimer. pH potentiometric results showed that H-bond

can form between the deprotonated tertiary amino groups and the dihydrogen-phosphate ions with $N_{(T)}H_2PO_4$ composition.

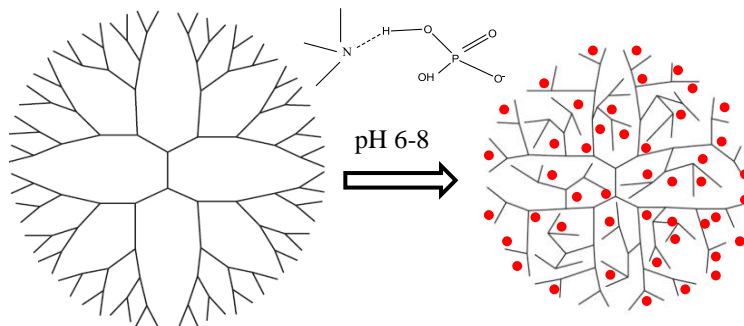


Figure 6. Structural changes of PAMAM dendrimer during the interaction with hydrogen- and dihydrogen phosphates.

We have pointed out that when $pH < 6$ and $pH > 8$ the relaxation of phosphate ions is the same as that of the free ions. They rather compensate the charge around the macromolecule, and do not affect the diffusion (size) of the dendrimer.

2.2. Ion pair formation of G5.NH₂ dendrimer with Au^{III} ions:

We have determined that the G5.NH₂ dendrimer forms ion pair with Au^{III} ions. Thus no complex formation occurs before the formation of dendrimer stabilized gold nanoparticles.

With the increasing concentration of Au^{III} ions ($[AuCl_x(OH)_{4-x}]$), resulting in more acidic medium, only the terminal (23, 24) CH₂ protons of the dendrimer showed smaller chemical shift values in the ¹H NMR spectrum at the given pH compared to the free dendrimer. The higher shielding indicates $-NH_3^+ - [AuCl_x(OH)_{4-x}]$ ion pairs in the system.

2.3. Interaction of functionalized dendrimers with doxorubicin (DOX):

Doxorubicin is non-covalently bound to the functionalized dendrimers and there is weak interaction between them. Relatively small amount of DOX could be incorporated into the solid preparatives.

We have pointed out that G5 PAMAM dendrimers functionalized with acetic acid (G5.Ac) and succinic acid (G5.SAH) significantly bound DOX molecules, while the dendrimer functionalized with glycidol (G5.GlyOH) interacted with less amount of doxorubicin.

We have proved that a part of the DOX molecules strongly binds to the G5.Ac and G5.SAH macromolecules, moves together with them. The chemical exchange process between the strongly and weakly bound or free DOX is slow on the ^1H NMR time scale thus separated peaks were detected. The strong interaction can be caused by H bond formation of deprotonated tertiary amines inside the dendrimers and the hydroxyl groups of DOX. In the case of G5.SAH the deprotonated carboxyl groups at neutral and alkaline pH can electrostatically interact with the DOX molecules of positive charge, but this interaction must be weak. The chemical exchange of weakly bound and free DOX is fast.

We have determined that a very small amount of drug can be incorporated in G5.GlyOH. A part of DOX moves with the dendrimer, but we couldn't characterize the interaction.

3. Interaction of G5.NH₂ dendrimer with colloids

3.1. Special stabilization of gold nanoparticles by G5.NH₂ dendrimers:

We have determined that 3 or 4 G5.NH₂ dendrimers stabilize one gold nanoparticle (AuNP), and the interaction is a transition between steric stabilization and encapsulation.

The interaction of G5.NH₂ with the 1.9-2.6 nm gold nanoparticles (studied at 25, 50, 75, 100 Au^{III}/G5.NH₂ ratios) occurs in the outer region

of the dendrimer, because the chemical shifts of the terminal protons in the macromolecule showed significant change in the ^1H NMR spectra of the samples. From the comparison of transmission electron microscopic and diffusion data we have concluded that in liquid phase there are gold-containing (hybrid nanoparticles) and free dendrimers in equilibrium. We have found fast exchange process in the ^1H NMR chemical shift time scale between the free dendrimers and the dendrimers in the hybrid particle.

From the average diffusion constant we have determined the size of the hybrid particle at different dendrimer – AuNP ratios. Comparing the results with the literature, we have concluded that the real size of these particles is 8-10 nm. In our explanation AuNPs are partially encapsulated into the dendrimers, which is supported by our ^1H NMR results, but several dendrimer molecules participate in the stabilization. Presumably 3 or 4 dendrimers stabilize one AuNP (Figure 7). This model is confirmed by our cryoporometry results detailed above.

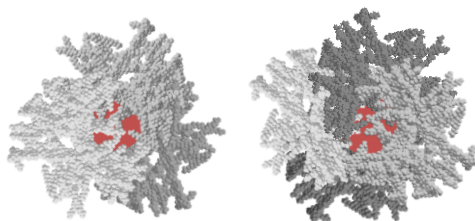


Figure 7. Gold nanoparticles stabilized by 3 and 4 G5.NH₂ dendrimers.

IV. POSSIBLE APPLICATIONS OF THE RESULTS

Results of my PhD thesis contribute to the different utilization of PAMAM dendrimers. For the encapsulation of drugs (therapeutic agents), delivery of contrast agents it is necessary to know the interaction with these molecules and also with the medium and the ions in it, and the effect of pH. The size of the dendrimer has a significant role in these utilizations, as well as during qualification methods, analytical protocols. Detailed knowledge of the colloid stabilizing effect of the fifth generation, most frequently used dendrimers contributes to the planning of nano-assemblies and the understanding of the nature of encapsulation.

The results show the use of a wide variety of NMR methods in the characterization of colloid systems, and investigation of non-dendritic polyelectrolyte macromolecules as well. Above macromolecules, NMR can be used to study colloidal dispersions as well, and NMR diffusometry could be installed into the practice of these investigations. We have proved that NMR cryoporometry can be used to determine the pore size distribution of soft materials.

V. LIST OF PUBLICATIONS

Papers related to the dissertation:

1. Mónika Kéri, Chen Peng, Xiangyang Shi and István Bányai
NMR characterization of G5_PAMAM.NH₂ entrapped atomic and molecular assemblies
The Journal of Physical Chemistry B, 2015 *Epub version, ahead of print*
(IP:3,377)
2. Zhang M, Guo R, Kéri M, Bányai I, Zheng Y, Cao M, Cao X, Shi X
Impact of dendrimer surface functional groups on the release of doxorubicin from dendrimer carriers.
The Journal of Physical Chemistry B, 2014, 118 (6), 1696-1706.
(IP:3,377)

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¹³C-NMR Analysis of Cellulose Samples of Different Preparation Methods
Cellulose, 2015 *Under revision* (IP:3,476)
2. István Bányai, Mónika Kéri, Zoltán Nagy, Márta Berka and Lajos P. Balogh
Self-diffusion of water and poly(amidoamine) dendrimers in dilute aqueous solutions
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3. Kéri Mónika: Milyen halból főzzünk halászlevet? (Hortobágyi halastavakból vett halminták ICP analízise)
Természet világa (Természettudományi Közlöny) 131.évf.8.sz. 2000
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PAMAM dendrimers in solution: Interactions with small molecules and ions
10th International Symposium on Applied Bioinorganic Chemistry, ISABC, 25-28 September, 2009, Debrecen, Hungary
2. István Bányai*, Mónika Kéri*, Zoltán Nagy, Márta Berka
Dynamics and Hydration of PAMAM_G5 dendrimers as PGSE NMR sees
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1. Kéri Mónika*, Nagy Zoltán, Bányai István, Balogh Lajos
PAMAM dendrimerek kölcsönhatása foszfát- és vanadátionokkal vizes oldatban
MTA Kolloidkémiai és Anyagtudományi Munkabizottsági Ülés, 2009. október 29-30., Mátrafüred
2. Bányai István*, Kéri Mónika, Nagy Zoltán, Balogh Lajos
Where are the phosphates in PAMAM_NH2 dendrimers?
Chemical Speciation in Solution and at Solid/Solution Interfaces, Symposium, 23-24 September 2010, Umeå University, Umeå, Sweden
3. Kéri Mónika
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4. Rácz András, Takács Anett, Kócs Tamara, Serra Bendegúz, Kéri Mónika, Tóth Imre, Bányai István*
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5. Prof István Bányai*, Mónika Kéri, prof Lajos Peter Balogh
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7. Kéri Mónika*, Bányai István
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XXXIV. Kémiai Előadói Napok, 2011. november 2-4. Szeged

8. Bányai István*, Kéri Mónika, Nagy Zoltán
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2012. évi NMR Munkabizottsági Ülés, 2012. május 4-5. Balatonszemes

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2013. évi NMR Munkabizottsági Ülés, 2013. május 9-10. Pécs

11. István Bányai*, Mónika Kéri, Krisztina László and Zoltán Nagy
Liquid NMR for solid state structures
DCIRM (Debrecen Colloquium on Inorganic Reaction Mechanisms), Debrecen, 2013.06.11-15.

12. M Kéri, C Peng, Z Nagy, X Shi, I Bányai*
Cavities in G5_PAMAM.NH2 Dendrimer. How do they exist?
8th International Dendrimer Symposium (IDS), Madrid, 2013.06.23-27.

13. Mónika Kéri, Zoltán Nagy, István Bányai*
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Mini - conference with Attila Szabo, 20 June 2014, Debrecen

14. Mónika Kéri*, István Bányai, Zoltán Nagy
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ECIRM (European Colloquium on Inorganic Reaction Mechanisms), 17-
20 June 2014, Debrecen

15. Kéri Mónika*, Xiangyang Shi, Nagy Zoltán, Bányai István
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vizsgálatok
MTA Kolloidkémiai Munkabizottság 2014. szeptember 25-26., Eger

16. Kéri Mónika*, Bányai István
Porózus anyagok jellemzése NMR krioporozimetria és diffúziometria
alkalmazásával
3. Környezetkémiai Szimpózium, 2014. október 9-10., Lajosmizse

* person presenting lectures or posters

List of publications:



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Subject: Ph.D. List of Publications

Candidate: Mónika Kéri
Neptun ID: UNIL0S
Doctoral School: Doctoral School of Chemistry
Mmt ID: 10047944

List of publications related to the dissertation

Foreign language scientific article(s) in international journal(s) (2)

1. **Kéri, M.**, Peng, C., Shi, X., Bányai, I.: NMR Characterization of PAMAM_G5.NH2 Entrapped Atomic and Molecular Assemblies.
J. Phys. Chem. B. Epub ahead of print (2015) ISSN: 1520-6106.
DOI: <http://dx.doi.org/10.1021/acs.jpcc.5b00272>
IF:3.377 (2013)
2. Zhang, M., Guo, R., **Kéri, M.**, Bányai, I., Zheng, Y., Cao, M., Cao, X., Shi, X.: Impact of Dendrimer Surface Functional Groups on the Release of Doxorubicin from Dendrimer Carriers.
J. Phys. Chem. B. 118 (6), 1696-1706, 2014. ISSN: 1520-6106.
DOI: <http://dx.doi.org/10.1021/jp411669k>
IF:3.377 (2013)





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List of other publications

Foreign language scientific article(s) in international journal(s) (1)

3. Bányai, I., **Kéri, M.**, Nagy, Z., Berka, M., Balogh, L.P.: Self-diffusion of water and poly(amidoamine) dendrimers in dilute aqueous solutions.
Soft Matter. 9 (5), 1645-1655, 2013. ISSN: 1744-683X.
DOI: <http://dx.doi.org/10.1039/c2sm26726h>
IF: 4.151

Total IF of journals (all publications): 10,905

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