Joint Laboratory of Solid-State NMR
IMC AS CR and JHIPC AS CR

WSSNMR

6.
Workshop on Solid-State NMR and Computational Methods

4. prosince 2012, Praha

Ústav makromolekulární chemie AV ČR, v.v.i.
Heyrovského nám. 2
162 06 Praha 6

Společná laboratoř NMR spektroskopie pevného stavu
ÚMCH AV ČR, v.v.i. a ÚJH AV ČR, v.v.i.

pořádají

dne 4.12.2012

V

klubu B
Ústavu Makromolekulární chemie AV ČR, v.v.i.
Heyrovského nám. 2, Praha 6

6.workshop NMR pevného stavu a souvisejících výpočtových metod

Program

9:30 - 10:00 **Spěváček Jiří**: Termoresponzivní polymery ve vodných roztocích studované NMR spektroskopií a dalšími metodami

10:00 - 10:30 **Starovoytová Larysa**: Effect of ketone- and ether-based additives on polymer globules formation

10:30 - 11:00 **Konefal Rafal**: NMR study of the additive-influenced poly(vinyl methyl ether) globule formation

11:00 - 11:20 přestávka na kávu

11:20 - 11:50 **Policianová Olívia**: Vplyv polymérnych matríc na štruktúru tuhých disperzií APIí: Prípadové štúdium kyseliny acetylsalicylovej v matriciach PVP, PEG, pHPMA a PEO.

11:50 - 12:20 **Kobera Libor**: Structural characterization of aluminosilicate polymers by solid state nmr: from initial phase to final product

12:20 - 12:50 **Urbanová Martina**: Structural diversity of trospium chloride: a comprehensive 13C CP/MAS NMR, DSC, FTIR and XRPD study.

12:50 - 13:30 přestávka na kávu a oběd

13:30 – 14:00 **Kříž Jaroslav**: Premicellar Interaction of PEO-PPO-PEO Triblock Copolymers with Partially Hydrophobic Alcohols

14:00 – 14:30 **Brus Jiří**: Zkoumání struktury polydopaminu pomocí NMR spektroskopie pevného stavu: izotopické obohacení 15N – drahý, ale efektivní postup.

14:30 Zakončení

16:00 neformální diskuse

TERMORESPONZIVNÍ POLYMERY VE VODNÝCH ROZTOCÍCH STUDOVANÉ NMR SPEKTROSKOPIÍ A DALŠÍMI METODAMI

Jiří Spěváček

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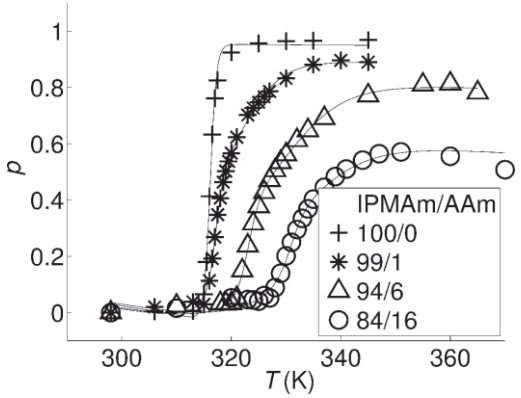
Je známo, že termoresponzivní polymery vykazují ve vodném roztoku fázovou separaci doprovázenou agregací a tvorbou tzv. mesoglobulí. Termosenzitivita činí tyto polymery zajímavé pro různé biolékařské a technologické aplikace, např. jako polymery pro uvolňování léčiv. V přednášce budou diskutovány výsledky získané nedávno u termoresponzivních polymerních systémů pomocí NMR a dalších metod (IČ spektroskopie, DSC). V první části bude porovnáno termoresponzivní chování poly(N-vinylkaprolaktamu) (PVKL) [1], což je polymer, který má poměrně značný aplikační potenciál, s chováním podstatně častěji studovaných akrylamidových polymerů. Byly zjištěny některé významné rozdíly, např. silná závislost přechodové teplotní oblasti na koncentraci PVKL roztoku, odlišný charakter molekul vody uvolňovaných z mesoglobulí s časem a zejména podstatně nižší stupeň dehydratace PVKL segmentů při teplotách nad fázovým přechodem. V druhé části budou prezentovány výsledky získané kombinací NMR a DSC při studiu teplotou-indukované fázové separace ve vodných roztocích statistických kopolymerů poly(N-isopropylmethakrylamid–akrylamid) (P(IPMAm-AAm)) [2]. Z těchto výsledků vyplývá, že s rostoucím obsahem AAm jednotek v kopolymeru se kooperativní jednotky vykazující fázový přechod zmenšují a výsledné globulární struktury jsou silně heterogenní. To může negativně ovlivnit účinnost statistických termoresponzivních kopolymerů obsahujících hydrofilní složku při některých aplikacích.

Poděkování: Autor děkuje za podporu GA ČR (projekt 202/09/1281).

[1] J. Spěváček, J. Dybal, L. Starovoytova, A. Zhigunov, Z. Sedláková, Soft Matter 8, 6110 (2012)
[2] J. Šťastná, L. Hanyková, J. Spěváček, Colloid Polym. Sci. 290, 1811 (2012)



Teplotní závislosti podílu IPMAm-jednotek s podstatně redukovanou pohyblivostí pro různá složení kopolymerů P(IPMAm-AAm) [2].

Effect of ketone- and ether-based additives on polymer globules formation

L. Starovoytova, J. Stastna, J. Kriz, R. Konefal, A. Sturcova, J. Dybal

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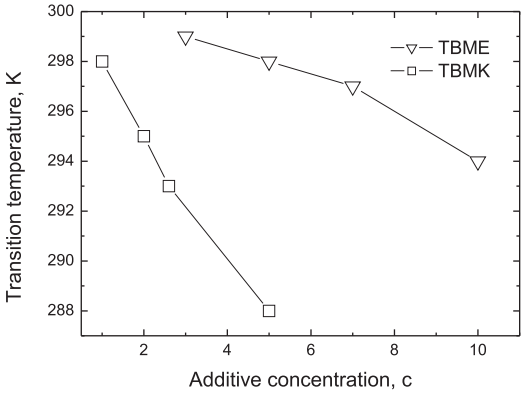
Difference in the influence of ketone-based additive from the ether-based one is obvious from the polymer concentration dependence of LCST. In case of ketone-based additives increasing of polymer concentration lead to the broadening of the transition. At the same time we observed that self-assembling starts at lower temperature and finish at higher temperature with polymer concentration increasing. Presence of ether-based additive leads to the shift of LCST to lower temperature and no broadening process was observed. Interaction with the polymer is strongly affected by the changing of hydrogen donor group of the additive.

On the other hand both ketone- and ether-based additives change the way of globules formation by pushing the water molecules out the globular structures, what leads to the formation of core inside the globular structure formed by polymer segments only. Shell of the globule is more porous and consists of three components: polymer segments, additive ad water molecules. Layer of additive/water molecule complexes attached to the surface of polymer globules protect the individual globules from interaction. This effect was observed by optical microscope and certified by the PFG NMR self-diffusion measurements and chemical exchange NMR experiments. This model can be confirmed by the cooling experiments where reorganization of the polymer globules is observed in two steps. First one corresponds to the re-solving process of the porous shell (~1-2K less than LCST), second step characterize the reorganization process in more rigid core part (require the lower temperature, 5-7K less than LCST). In such a structure no effect of water releasing observed, only releasing of a small part of an additive is taking place.



NMR study of the additive-influenced poly(vinyl methyl ether) globule formation

Rafał Konefał, Larisa Starovoytova

Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic

It's well known that poly(vinyl methyl ether) (PVME), exhibit in aqueous solutions lower critical solution temperature (LCST) behavior. PVME is soluble below the LCST, but heating above lower critical solution temperature results in phase separation (coil-globule transition), which is visible by the milk-white turbidity of the solution [1].
In this contribution the phase separation of PVME (0,5% and 5% wt.) is studied under the influence of small organic additives: 3,3-dimethyl-2-butanone, 3-methyl-2-butanone, 2-butanone. The LCST is determined by 1H-NMR spectroscopy. Additives shift down the lower critical solution temperature, which depends on additive and additive concentration. Measurements spin-spin relaxation time T2 of water and additives provide information about behavior of water and additives in globule state in temperature above LCST.

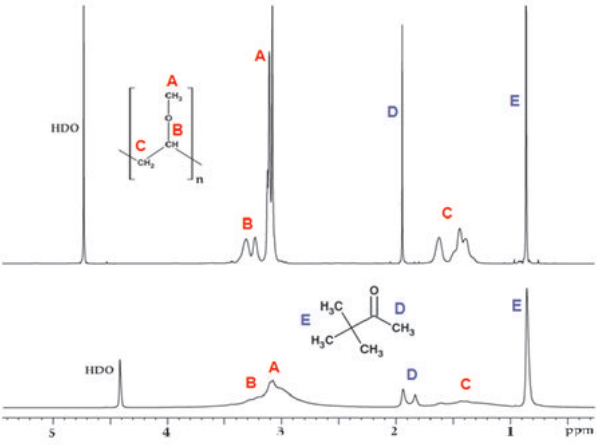


Figure 1. 1H-NMR spectrum of sample: 5% PVME 5% 3,3-dimethyl-2-butanone; below (top), and above (down) LCST.

References:

1. Aseyev VO, Tenhu H, Winnik FM. Adv Polym Sci 2006;196:1-85

Abstrakta P4

Vplyv polymérnych matríc na štruktúru tuhých disperzií APIí: Prípadové štúdium kyseliny acetylsalicylovej v matriciach PVP, PEG, pHPMA a PEO.

Olívia Policianová

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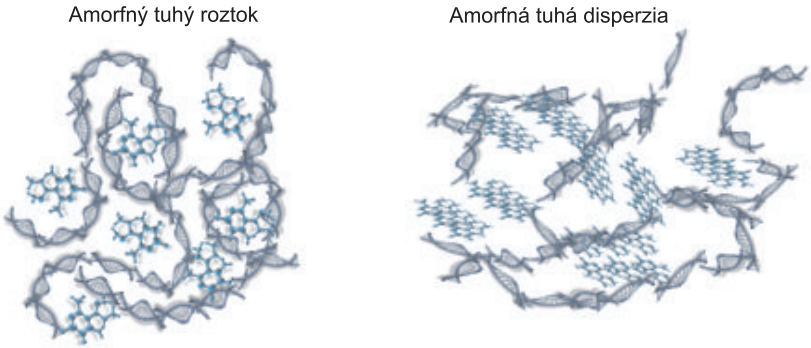
Aktuálnym vývojovým trendom farmaceutických spoločností je snaha o zvyšovanie biodostupnosti substancií s nízkou biodostupnosťou rôznymi metódami. Jednou z nádejných metód je i tvorba tuhých disperzií. Na vplyv štruktúrnych a farmakokinetických vlastností týchto disperzií má okrem výberu vhodnej metódy, či premeny ich vzniku aj matrica (polymér, celulósa, močovina atd.), do ktorej sa API disperguje. V tomto príspevku je prezentované štúdium vplyvu rôznych polymérnych matríc (PEG, PVP, pHPMA a PEO (poly(2-etyl-2-oxazolín)) a ich molekulových hmotností na tvorbu (Obr. 1.) a vlastnosti tuhých disperzií kyseliny acetylsalicylovej pomocou ssNMR. K štruktúrnej analýze disperzných systémov boli použité experimenty 13C CP/MAS NMR, 1H DQ-BABA a relaxačné experimenty. K sledovaniu zmien disolučných rýchlostí tuhých disperzií a ich fyzikálnych zmesí in vitro (37˚C) bola použitá metóda disolučných profilov.



Obr.1: Prípadné formulácie API-polymér tuhých disperzií

Structural characterization of aluminosilicate polymers by solid state NMR from initial phase to final product

Libor Kobera, Jiri Brus

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Current trend in alumino silicate chemistry is to develop new types of materials with low energy requirements but still possessing good mechanical properties. One of the possibilities is preparation amorphous aluminosilicate polymers by alkali activation of calcinated aluminosilcate layered minerals at the room temperature.

Modification of inorganic matrix provides new possibilities of material research and properties improvements. Epoxy resin was used for structural modification (combination of (3-aminopropyl) trimethoxysilane with Bisphenol A diglycidyl ether) that decreases water permeability and material cracking. However, modification of primary non-crystalline aluminosilicate structure is accompanied with creating very complicated organo-inorganic heterogeneous network.

An understanding and disclosure of the fine relations between structure, processing and post-processing of various types of amorphous aluminosilicate polymers requires application of carefully designed and optimized techniques of solid-state NMR spectroscopy. In our work, we focussed our attention to the initial phases of matrix formation. To gain structural information provided by solid-sate NMR we used not only simple one-dimensional experiments (MAS) on various nuclei like 1H, 13C, 23Na, 27Al, 29Si but also two-dimensional multiple-quantum experiments (27Al 3Q/MAS NMR) for detailed description of these systems. Spectra of multi-quantum experiments were finally processed by biaxial shearing, which can uncover small structural details and provide new information about structural fragments.

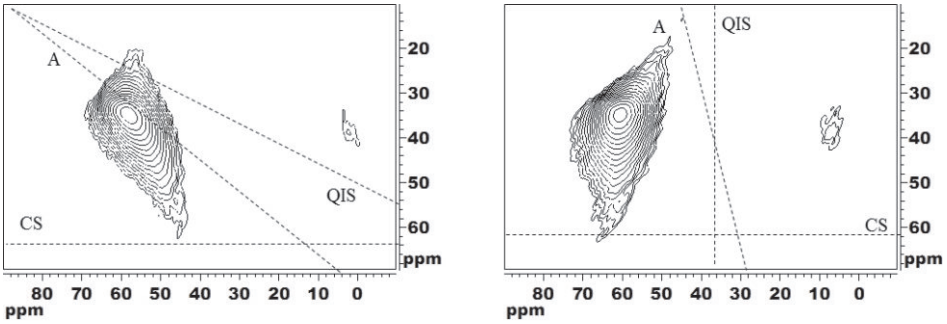

Figure . Q-sheared and biaxially sheared 27Al MQ/MAS NMR spectra of stable inorganic aluminosilicate polymer

Structural diversity of trospium chloride: a comprehensive 13C CP/MAS NMR, DSC, FTIR and XRPD study

Martina Urbanová

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Despite advances in solid-state analysis, structural characterization of active pharmaceutical ingredients is a complex problem that requires combination of many experimental approaches. Detailed analysis of 13C CP/MAS NMR, DSC, FTIR and XRPD data of a range of trospium chloride products prepared under different crystallization conditions confirmed that the crystals exhibit different degree of disorder, rather than traditional polymorphism. While 13C CP/MAS NMR spectra clearly demonstrated considerable structural diversity of crystalline powders of trospium chloride, temperature-modulated DSC indicated two-component character. FTIR spectra revealed alterations in the hydrogen bonding network (ionic hydrogen bond formation), whereas the X-ray diffraction confirmed basically unchanged unit cell parameters. Therefore, all the investigated trospium chloride powders crystalized from ethanol under various conditions can be considered as one polymorphic form with partly separated domains that slightly differ from each other in the degree of molecular disorder, in the quality of crystal lattice and hydrogen bonding network. It is demonstrated that, for the quality control of complex products for which standard approaches fail, 13C CP/MAS NMR spectroscopy combined with factor analysis can satisfactorily be used for categorizing the individual samples: factor analysis of 13C CP/MAS NMR spectra found clear relations between the extent of molecular disorder and crystallization conditions.

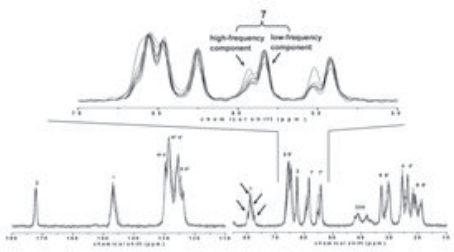

Figure 1. Overlay of 13C CP/MAS NMR spectra of the investigated samples of trospium chloride.

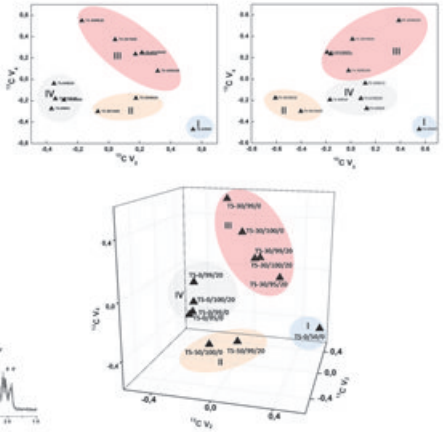

Figure 2. 2D and 3D correlation graphs for coefficients (scores) Vi2, Vi3 and Vi4 calculated from the 13C CP/MAS NMR spectra and relevant subspectra

Premicellar Interaction of PEO-PPO-PEO Triblock Copolymers with Partially Hydrophobic Alcohols

Jaroslav Kříž

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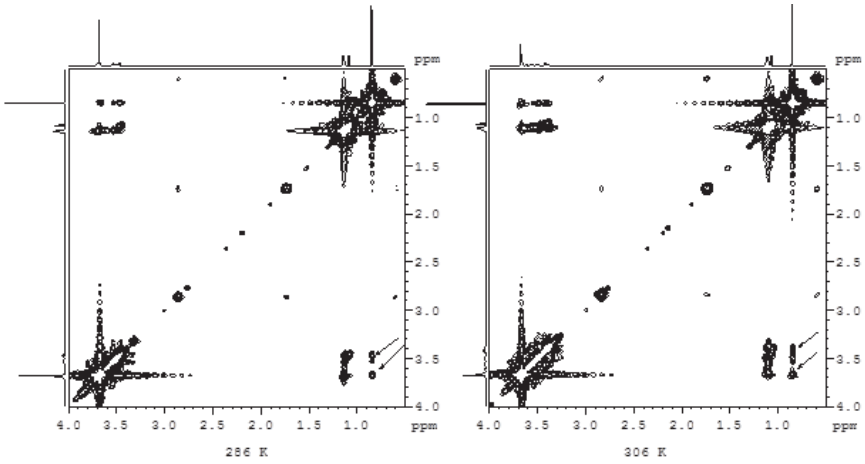
The interactions of 2-butanol (BuOH), 3-methyl-2-butanol (MeBuOH) and 3,3-dimethyl-2-butanol (Me2BuOH) with propylen oxide octamer (PO8) and the copolymers (EO)8(PO)13(EO)8 (L35) and (EO)13(PO)30(EO)13 (L64) in D2O were studied using 13C NMR spectra and relaxations and 1H PFG NMR diffusion measurements. For L64, the temperature of conformation change decreases by 6 K for each additional methyl group in the alcohol. The first signs of L64 aggregation are at temperatures 7, 10, and 13 K lower for BuOH, MeBuOH and Me2BuOH, respectively. These effects are much weaker for (PO)13 in L35 or nonexistent for (PO)8 in PO8 showing thus the role of cooperativity in dehydration and aggregation processes. The molar fraction of the alcohol hydrogen-bonded to L64 increases with its hydrophobicity and with increasing temperature at which also higher NOE can be observed. Strong hydrogen bond interaction, which is in mutual cooperation with hydrophobic interaction, does not preclude the exchange between bound and free states of the alcohol, however. Using 13C transverse relaxation, its correlation time is shown to be of the order of 10 microseconds.



NOESY spectra of the system of 10 %w/w L64 and 4 %w/w of Me2BuOH in D2O at indicated temperatures (cross-peaks indicating dipolar interaction between the methyl protons of the additive and the CH and CH2 protons of PPO are marked by arrows).

Abstrakta P8

Zkoumání struktury polydopaminu pomocí NMR spektroskopie pevného stavu: izotopické obohacení 15N – drahý, ale efektivní postup.

Jiří Brus

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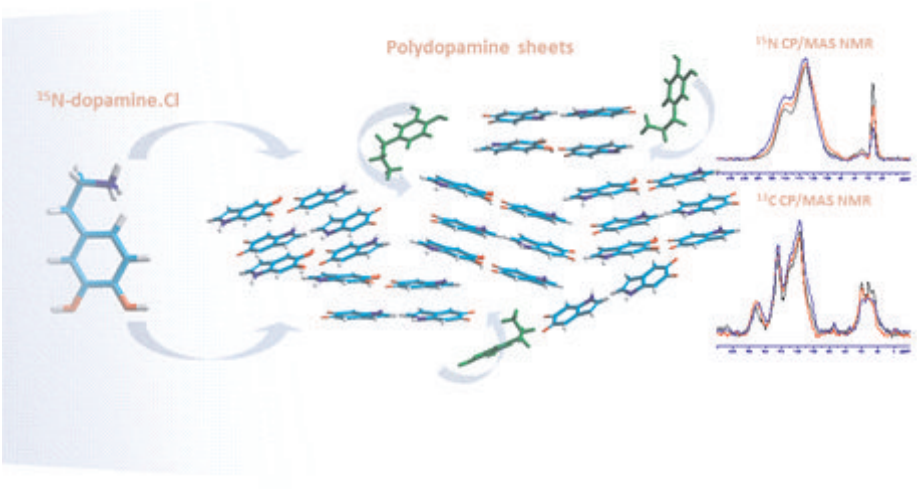
e-mail: brus@imc.cas.cz

V roce 2012 jsme se mimo jiné věnovali ve spolupráci kolegou V. Proksem zkoumání struktury a strukturních polydopaminových vrstev, ke kterým dochází během termálního namáhání. V literatuře existuje řada hypotéz, které se pokouší popsat mechanismus konverze dopaminu chloridu na nerozpustný polymerní produkt. Některé zahrnují pouze intramolekulární cyklizaci spojenou s dehydrogenací a vznikem vodíkových můstků mezi hydroxylovými a chinonovými skupinami, jiné předpokládají vznik chemických vazeb mezi dopaminovými segmenty. Pro získání základních informací o mechanismu vzniku polydopaminu a jeho následné termální stabilizace jsme se rozhodli využít NMR spektroskopie pevného stavu. Je zřejmé, že vedle 13C CP/MAS NMR jsou významným nositelem strukturních informací 15N CP/MAS NMR spektra. Získání kvalitních spekter v přirozeném izotopickém zastoupení je však v případě polydopaminu realizovatelné v časovém horizontu několika dní. Měření 2D spekter je zcela nerealizovatelné. Proto jsme přistoupili k izotopickému obohacení dopaminu. To bylo sice nákladné (100.000 Kč/gram), nicméně jsme získali velmi kvalitní 15N CP/MAS NMR spektra, ve kterých jsme identifikovali 7 různých strukturních jednotek, které jsme pomocí nově vyvinuté metody měření 15N CPPI profilů dokázali přiřadit základním strukturním jednotkám. Posléze v kombinaci s 1H-13C a 1H-15N HETCOR spektry jsme získali detailnější informace o struktuře tohoto nerozpustného, černého a na první pohled odpudivě vyhlížejícího materiálu, který však má velký potenciál pro povrchové modifikace.



Postery

NMR crystallography – structure refinement (simvastatin)

Jiri Brus*, Martina Urbanova*, Olivia Policianova*, Michal Husak**

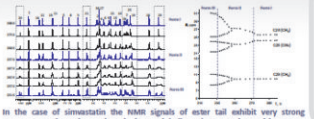
*) Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic
**) Institute of Chemical Technology of Prague, Department of Solid State Chemistry, Czech Republic

ss-NMR

While thermodynamics of any crystal-phase transition is described by DSC, solid-state NMR spectroscopy provides site-specific information about these events at atomic resolution without requirements on long-range order.

Chemical shifts – VT ^{13}C CP/MAS NMR

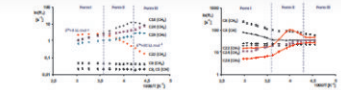
Variable-temperature NMR experiments clearly identify molecular fragments that are most affected by the crystal-phase transition.



In the case of simvastatin the NMR signals of ester tail exhibit very strong temperature dependence, broadening and bellow the second transition steep narrowing. While the crystal Form II is rather motionally disordered, Form III consists of two symmetry independent molecules with well defined conformations.

Motional frequencies – VT T_1 relaxation

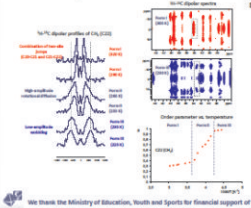
Molecular dynamics substantially affects physical properties of many organic solids. T_1 and $T_{1\rho}$ NMR relaxation measurements provide valuable information about segmental dynamics in wide range of correlation times.



As indicated by very short T_1 relaxation times the ester tail carries out fast (high-frequency) motion that is substantially restricted by the first transition. The mid-kilohertz motional mode of the ester tail is strongly affected by both transitions, and activation energy of theses motions dramatically change.

Motional amplitudes

Amplitudes of segmental motions can be probed by measurements of one-bond ^{1}H-^{13}C dipolar couplings. The determined order parameter can be converted to motional amplitudes. High-amplitude motions of the ester tail (C22) are dramatically reduced: Form I → Form III.

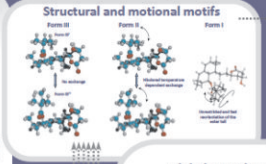


We thank the Ministry of Education, Youth and Sports for financial support of Czech Republic (grant No.2B08021).

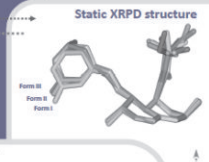
NMR crystallography

The concept of NMR crystallography – a combination of advanced techniques of solid-state NMR, x-ray powder diffraction and molecular computation – is applied to describe structure and molecular dynamics of the recently discovered low-temperature crystal modifications of simvastatin.

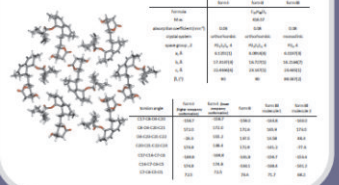
Structural and motional motifs



Static XRPD structure

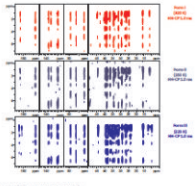


Global crystal packing for simvastatin: Form I, Form II and Form III



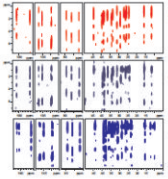
^{1}H-^{13}C contacts
FSLG HHCP HETCOR

Proton-carbon spin pairs are detected by 2D HETCOR experiments. Sufficient resolution allows to identify more than 80 heteronuclear contacts.



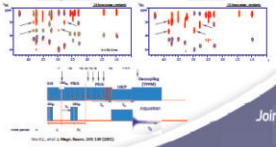
^{1}H-^{13}C contacts
FSLG LGCP HETCOR

A bit different correlation pattern is provided by HETCOR experiments in which ^{1}H-^{1}H spin exchange is suppressed by Lee-Goldburg cross-polarization.



Long-range ^{1}H-^{13}C contacts
REDOR-dephased HETCOR

Suppression of one-bond correlation signals increases the number of structurally more important long-range contacts.
Form I: 25 → 40; Form II: 27 → 43; Form III: 31 → 49.



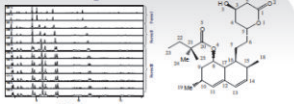
XRPD

X-ray diffraction on single crystals provides the "golden standard" of molecular structure analysis. In absence of suitable single crystals the diffraction on powdered samples (XRPD) is applied. Structure determination, however, is not straightforward even from synchrotron data. Distance restraints and structural fragments obtained by ss-NMR then can provide initial models for the structure refinement.

Simvastatin

While atorvastatin (the world's best selling drug) exhibits extensive polymorphism including more than 65 solid forms, simvastatin is still described only in one anhydrous crystalline form. But according to the McCrone's famous statement other crystal forms of simvastatin must exist.

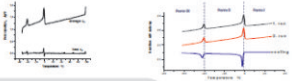
Diffractograms - VT XRPD



There are only slight differences between all three phases, but the differences still significantly affect the powder diffraction pattern. From the terminology point of view it would be interesting to discuss, if such slight conformation changes accompanying the phase transformation I → II are enough to consider the change as a true phase transformation or a change of disorder with the identical phase. The energy changes occurring during this process seem to indicated true crystal-phase transition.....

Differential Scanning Calorimetry

DSC plots show two endothermic events occurring at 232.6 and 272.0 K. Low enthalpy of both events (ΔH = 1.1 and 2.7 J/g) indicates that both crystal phase transitions do not dramatically change potential energy of the system (weak interactions and segmental dynamics are affected).



Joint Laboratory of Solid-State NMR
IMC AS CZ and JHIPC AS CZ

Influence of polymeric matrices on the structure of solid dispersions of APIs: A case study of acetylsalicylic acid in PVP, PEG, pHPMA and PEO

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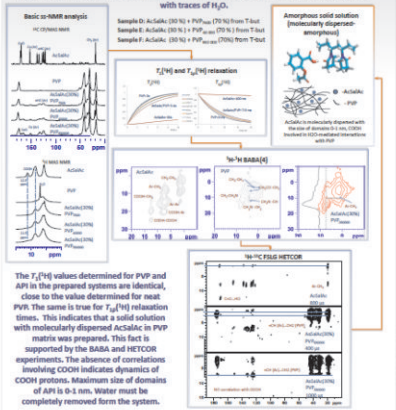
Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, Heyrovského nám. 2, 162 06 Praha 6, Czech Republic,

1. Acetylsalicylic acid (AsSalAc) in PVP matrix

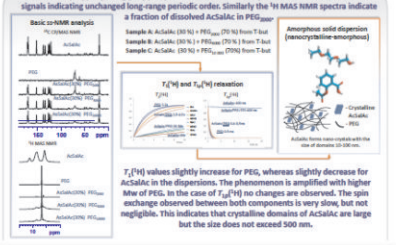
AcSalAc in poly(vinylpyrrolidone) matrix is characterized by the broad ^{13}C CP/MAS NMR signals indicating loss of molecular periodic order. The ^{1}H MAS NMR spectra, in particular the signal of COOH protons moved from 12.5 to 11.5 ppm indicates that hydrogen bonding is slightly weakened. Broadening of the signal indicates irregularities in the strength of H-bonding or chemical exchange with traces of H_2O.



The T_1[^{1}H] values determined for PVP and API in the prepared systems are identical, close to the value determined for neat PVP. The same is true for $T_{1\rho}$[^{1}H] relaxation times. This indicates that a solid solution with molecularly dispersed AcSalAc in PVP matrix was prepared. This fact is supported by the BABA and HETCOR experiments. The absence of correlations involving COOH indicates dynamics of COOH protons. Maximum size of domains of API is 0-1 nm. Water must be completely removed form the system.

2. Acetylsalicylic acid in PEG matrix

AcSalAc in poly(ethylene glycol) (PEG) matrix is characterized by the narrow ^{13}C CP/MAS NMR signals indicating unchanged long-range periodic order. Similarly the ^{1}H MAS NMR spectra indicate a fraction of dissolved AcSalAc in PEG$_{MW}$.

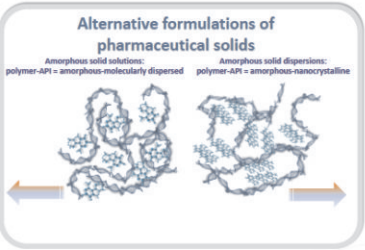


T_1[^{1}H] values slightly increase for PEG, whereas slightly decrease for AcSalAc in the dispersions. The phenomenon is amplified with higher Mw of PEG. In the case of $T_{1\rho}$[^{1}H] no changes are observed. The spin exchange observed between both components is very slow, but not negligible. This indicates that crystalline domains of AcSalAc are large but the size does not exceed 500 nm.

Introduction

In our work we focused on the study of structural properties of formulated as solid dispersions. As a model API we used acetylsalicylic acid (AcSalAc) that exhibits low solubility, low toxicity, limited polymorphism, low chemical stability (easy hydrolysis) and limited molecular flexibility (extremely rigid molecule). As polymer matrices we tested polyvinylpyrrolidon (PVP), poly [N-(2-hydroxypropyl)metacrylamide] (pHPMA), poly(2-ethyl-2-oxazoline) (PEO) and polyethylene glycol (PEG). Lyofilization (lyo) was used to combine both components. The polymers were used with different molecular weight. As solvents we used nontoxic and biodegradable compounds, which solubilize API and polymer matrix as water, ethanol and tert-butanol (T-but). Polymers were dried before the lyofilization and the prepared samples were redried.

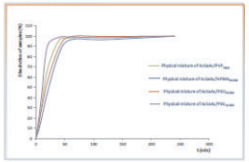
Alternative formulations of pharmaceutical solids



5. Dissolution profiles

The bioavailability of drug is assumed to be determined by its dissolution process in human fluids (body fluid, stomach and intenstine fluid,...). To study this process in vitro (37°C) were used the method of dissolution profiles of drug release from formulations. It was selected one system exhibiting the best relaxation time from each tested polymer matrices with API to create physical mixtures.

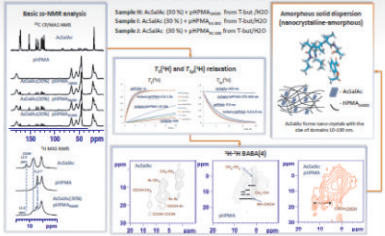
Physical mixtures of AcSalAc/PEG appears the fastest dissolution rate than others. For next studies dissolution results of physical mixtures will be compared with created solid dispersions of AcSalAc referred here. We suppose better dissolution rate for solid dispersions.



Dissolution profiles of physical mixtures were tested in dissolution media – phosphate buffer at pH 7,4 simulated body fluid (500ml) with using shaker with incubator. Dissolution samples were collected at 5, 10, 20, 40, 60, 120 and 240 min through 0,22 μm filters and analyzed by UV/VIS measure at 225 nm.

3. Acetylsalicylic acid in pHPMA matrix

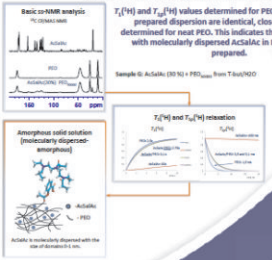
AcSalAc in poly[N-(2-hydroxypropyl)metacrylamide] (HPMA) matrix is characterized by the narrow ^{13}C CP/MAS NMR signals indicating nearly unchanged long-range periodic order. Similarly the ^{1}H MAS NMR spectra indicate only slight changes in global molecular arrangement of AcSalAc.



The T_1[^{1}H] values determined for pHPMA and API in the prepared dispersions are different. The T_1[^{1}H] of AcSalAc, however, is significantly shortened to about 15-30 s (from 60s). This indicates partial equilibration through spin diffusion. In the case of $T_{1\rho}$[^{1}H] relaxation times no equilibration is observed. This indicates that AcSalAc forms crystalline nanodomains in pHPMA matrix. Higher Mw induces reduction of the domain size. BABA experiments indicates certain kind of molecular interaction (on the surface?) between AcSalAc and pHPMA segments.

4. Acetylsalicylic acid in PEO matrix

AcSalAc in poly(2-ethyl-2-oxazoline) (PEO) matrix is characterized by the broad ^{13}C CP/MAS NMR signals indicating loss of molecular periodic order.



T_1[^{1}H] and $T_{1\rho}$[^{1}H] values determined for PEO and AcSalAc in the prepared dispersion are identical, close to the values determined for neat PEO. This indicates that a glass solution with molecularly dispersed AcSalAc in PEO matrix was prepared.

Joint Laboratory of Solid-State NMR IMC AS CZ and JHIPC AS CZ

Deep Insight into the Structure of Organo-modified Aluminosilicate Polymers by Solid State NMR: From Initial Phase to Final Product

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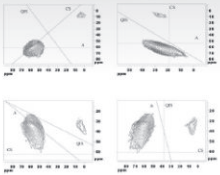
Aluminosilicate Inorganic Polymers

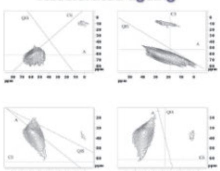
Preparation of Amorphous Inorganic Polymers (AIP`s) involves the chemical reaction of calcinated aluminosilicates with alkali activated water glass (metasilcate) that results into amorphous polymeric Si-O-Al matrix. In some cases, these amorphous systems, prepared by NaOH activation undergoes crystallization transformation which is accompanied by loss of starting mechanical properties.

Modification of aluminisilicate matrix, by epoxy resin - *in situ*, decreases volume porosity, which is one of crucial factor for mechanical properties. It can be suppose, that lower volume porosity, will stop crystallization transition and loss of original properties.

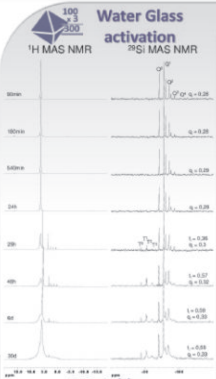
Shearing transformation ^{27}Al MQ/MAS NMR



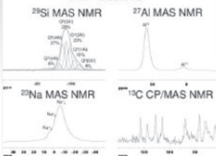
Accelerated ageing



Water Glass activation



AIP stable



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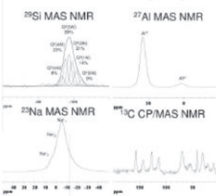
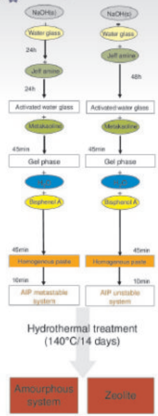
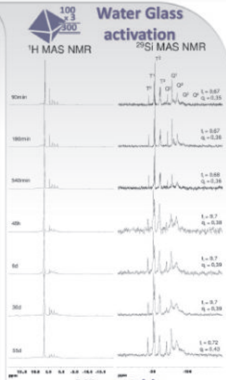


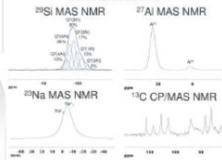
Experimental



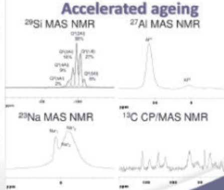
Water Glass activation



AIP unstable



Accelerated ageing



Conclusion

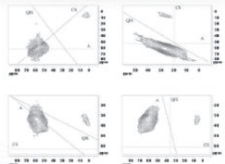
Structural stability of AIP systems can be controlled by the method of manufacture, while maintaining the overall chemical composition. It appears likely that the crucial step is activation of water glass, i.e. the moment of (3-amino propyl) trimethoxysilane addition into the reaction mixture.

Standard 1D MAS NMR experiments of prepared species did not provided sufficient spectral resolution to identify structural differences between stable and unstable systems, before aging. Therefore, high sensitive ^{27}Al MQ/MAS NMR experiments combined with sophisticated shearing transformation had to be used to uncover slight structural differences.

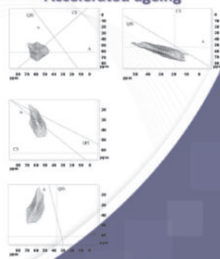
Shearing transformation

Amorphous or disordered materials typically give a distribution of chemical shifts and/or quadrupolar parameters, it can be more difficult to interpret 2D MQ/MAS NMR spectra to identify distinct chemical sites. Therefore, sophisticated methods of 2D MQ/MAS NMR spectra processing had to be used to obtain detailed structural information. This procedures are called as ISO-Q-shearing, biaxial ISO- and biaxial Q-shearing.

Shearing transformation ^{27}Al MQ/MAS NMR



Accelerated ageing



Joint Laboratory of Solid-State NMR
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Combined polymorphism and structural disorder of Trospium Chloride as seen by ^{13}C CP/MAS NMR, XRPD, FTIR and DSC

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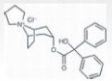
Introduction

Despite recent advances in solid-state NMR spectroscopy, structural characterization of amorphous and disordered active pharmaceutical ingredients (APIs) is a complex problem that requires a combination of many experimental approaches. In some cases even small changes in the structure result in significant variation in drug dissolution rate or stability. Exact identification of different solid-state forms and description of their disorder is crucial to anticipate changes in physicochemical behavior of the pharmaceutical solids. In this contribution, we present our recent investigation of trospium chloride ($C_{25}H_{30}ClNO_3$), a quaternary amine with anticholinergic properties, which is used for the treatment of overactive bladder. Trospium chloride is a typical representative of complex systems exhibiting a considerable degree of molecular disorder combined with extensive polymorphism. In addition, in many cases trospium chloride does not form single-form product. Rather a mixture of very similar crystal modifications is usually created.

Experimental

Materials: Trospium chloride ($C_{25}H_{30}ClNO_3$; Scheme 1) was used as received from Interpharma, Prague, Czech Republic.



Structural formula of trospium chloride ($C_{25}H_{30}ClNO_3$) and marking of specific structure units.

Preparation of sample – recrystallization: Samples were prepared by recrystallization of powdered trospium chloride. Different mixtures of water and ethanol (@(EtOH)=c; 0, 99; 0,95; 0,9) were used as a solvent. Besides the amount of water in the solvent, there were two other conditions in which the samples differed: i) crystallization temperature (0°C, 20°C) and ii) initial concentration of solution (saturated solution, 30% and 50% excess of solvent).

Methods:

Solid-state NMR spectra were measured using a Bruker Avance 500 NMR spectrometer. Magic angle spinning (MAS) frequency was 11 kHz for ^{13}C. Amplitude modulated cross-polarization (CP) of 2 ms duration was used to obtain ^{13}C CP/MAS NMR spectra. The repetition delay was 30 s. The ^{13}C scale was calibrated with glycine as external standard (176.03 ppm – low-field carbonyl signal).

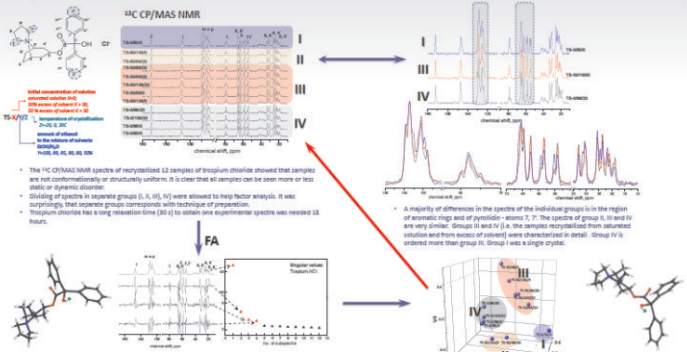
Differential scanning calorimetry (DSC) measurements were carried out on a DSC calorimeter 8500 (PerkinElmer, USA) with a nitrogen purge gas. The instrument was calibrated for temperature and heat flow using indium as a standard. Heat capacity readings were calibrated using sapphire. Samples were encapsulated into closed aluminium pans and sample massed of 2 – 3 mg were used. The sample was heated to 150 °C with heating rate 10 °C / min and tempered 3 min at 150 °C. Then, the sample was heated using the StepScanTM DSC measurement combining short heating steps with isotherms (heating rate 3 °C / min and isothermal segment 2 min) up to 254 °C. Data acquisition and analysis were performed using the Pyris Manager software.

Statistical Analysis: Factor Analysis and Spectral Pretreatment: Factor analysis (FA) using the singular value decomposition (SVD) algorithm was performed to extract information from the experimental data obtained by ^{13}C CP/MAS NMR and XRPD data, and to visualize differences between various forms of the API. Processing of spectral data was performed using Matlab program package. The following spectral range was subjected to the factor analysis: ^{13}C CP/MAS NMR: from 180 to 0 ppm. All ^{13}C CP/MAS NMR NMR spectra were base-line corrected and normalized. Preparation and processing of a moderately sized data set containing ca. 12 spectra took about 10 min.

IR Experiments: The ATR FTIR spectra were recorded on Thermo Nicolet NEXUS 870 FTIR Spectrometer with a MCT detector. Single reflection ATR accessory Golden Gate (Specac, UK) with diamond crystal was used. Spectral resolution was 4 cm^{-1} with 256 scans taken for each spectrum. Spectral region between 1700 and 2600 cm^{-1} strongly affected by absorption of diamond ATR crystal were cut off. The spectra were normalized to compensate the variations of pressure between the sample and ATR crystal.

We thank Czech Science Foundation (Grant No. P106/11/P426) for financial support.

Results – ssNMR spectroscopy and Factor analysis



- The ^{13}C CP/MAS NMR spectra of recrystallized 12 samples of trospium chloride showed that samples are not conformationally or structurally uniform. It is clear that all samples can be seen more or less static or dynamic disorder.
- Dividing of spectra in separate groups (I, II, III, IV) were allowed to help factor analysis. It was surprisingly, that separate groups corresponds with technique of preparation.
- Trospium chloride has a long relaxation time (30 s) to obtain one experimental spectra was needed 18 hours.

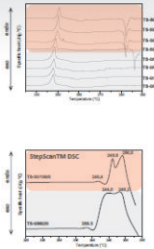
- A majority of differences in the spectra of the individual groups is in the region of aromatic rings and of pyrrolidin - atoms 7, 7'. The spectra of group II, III and IV are very similar. Groups III and IV (i.e. the samples recrystallized from saturated solution and from excess of solvent) were characterized in detail. Group IV is ordered more than group III. Group I was a single crystal.

Conclusion

Polymorphism and disordered structures of trospium chloride are reflected by very complex spectroscopic data, including XRPD, FTIR and ^{13}C CP/MAS NMR spectra, which are difficult to interpret. Therefore, we tried to solve this problem by combining spectroscopic data with factor analysis. It is demonstrated that ^{13}C CP/MAS NMR spectroscopy combined with factor analysis (SVD algorithm) and with the assistance of DSC and FTIR offers a reliable tool to distinguish various disordered forms of trospium chloride and to understand its structural variability.

- Only the combination of ^{13}C CP/MAS NMR and FA was able to clearly divide the spectra into three groups.
- The groups III and IV are very similar. Deconvolution of ^{13}C CP/MAS spectra showed, that there are two crystal modifications, which - in groups III and IV, are represented in a different ratio. In addition, there is also a certain amount of amorphous or disordered phase in both groups.
- StepScanTM DSC giving an evidence of two main crystalline forms in groups III and IV.
- In group IV, FTIR analysis and a detail in the processed spectra showed greater number of ionic hydrogen bonds between the OH group and the chloride anion. This characteristic may distinguish two polymorph forms.

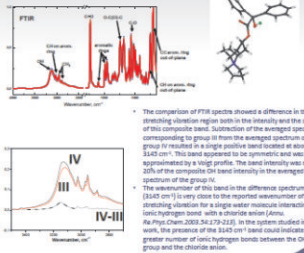
DSC



- The comparison results od DSC showed, that group IV has melting point (ca.248°C) and group III (ca.251°C). The DSC measurement was complicated by the fact that the samples started to degrade immediately after the melting, even in the inert nitrogen atmosphere. The degradation of group III and group IV is different. The degradation connected with rapid weight decreasing was also confirmed by thermogravimetric analysis.

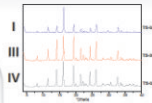
- For the both groups III and IV , a large endotherm of melting splitted into two peaks was observed, giving an evidence of two main crystalline forms. In the case of group IV was not well separated. It meant the presence of crystalline forms with similar structure conformation. Differences were observed in the group III. An onset of the endothermic melt was shifted to higher temperature and the both endothermic peaks (with maxima at 246 °C and 251 °C) were more separated. The maximum of first peak was observed at the same position whereas the maximum of second peak was significantly shifted to higher temperature. This indicated a presence of more developed crystals from the macroscopic point of view. But at molecular level the presence of less and more developed crystals in the sample led to an extent of disorder.

FTIR



- The comparison of FTIR spectra showed a difference in the OH stretching vibration region both in the intensity and the shape of this composite band. Subtraction of the averaged spectrum corresponding to group III from the averaged spectrum of group IV resulted in a single positive band located at about 3143 cm^{-1}. This band appeared to be symmetrical and was best approximated by a Voigt profile. The band intensity was about 30% of the composite OH band intensity in the averaged spectrum of the group IV.
- The wavenumber of this band in the difference spectrum (3145 cm^{-1}) is very close to the reported wavenumber of OH stretching vibration for a single water molecule interacting via ionic hydrogen bond with a chloride anion (*Annu. Re Phys.Chem.2003.54:173-213*). In the system studied in this work, the presence of the 3145 cm^{-1} band could indicate greater number of ionic hydrogen bonds between the OH group and the chloride anion.

XRPD



- The XRPD no showed a difference in the diffractograms. Processing of diffractograms by factor analysis of records returned no results.

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Seznam publikací za rok 2012

Publikace vyšlé

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27Al magic angle spinning–nuclear magnetic resonance (MAS-NMR) analyses applied to historical mortars
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- Brus J., Kobera L., Urbanová M., Koloušek D., Kotek J.
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- Kříž J.
Interaction of premicellar states of a PEO-PPO-PEO triblock copolymer with partially hydrophobic substances: NMR study
Journal of Physical Chemistry B. Roč. 116, č. 14 (2012), s. 4386-4393

- Spěváček J., Dybal J., Starovoytová L., Zhigunov A., Sedláková Z.
Temperature-induced phase separation and hydration in poly(N-vinylcaprolactam) aqueous solutions: a study by NMR and IR spectroscopy, SAXS, and quantum-chemical calculations
Soft Matter. Roč. 8, č. 22 (2012), s. 6110-6119

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Preparation of novel, nanocomposite stannoxane-based organic-inorganic epoxy polymers containing ionic bonds
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- Jager A., Gromadzki D., Jager E., Giacomelli f. C., Kozlowska A., Kobera L., Brus J., Říhová B., El fray M., Ulbrich K., Štěpánek P.
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Polyacetylene-type networks prepared by coordination polymerization of diethynylarenes: new type of microporous organic polymers
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- Kobera L., Urbanová M., Brus J.
Více-kvantová NMR spektroskopie pevného stavu: způsob jak nahlédnout do struktury anorganických materiálů
Chemické listy. Roč. 106, č. 9 (2012), s. 802-808

- Chlupatý T., Padělková Z., Lyčka A., Brus J., Růžička A.
Reactivity of lithium n-butyl amidinates towards group 14 metal(II) chlorides providing series of hetero- and homoleptic tetrylenes
Dalton Transactions. Roč. 41, č. 16 (2012), s. 5010-5019

- Kříž J., Dybal J., Makrlík E., Kohnke f. H.
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Konferenční příspěvky
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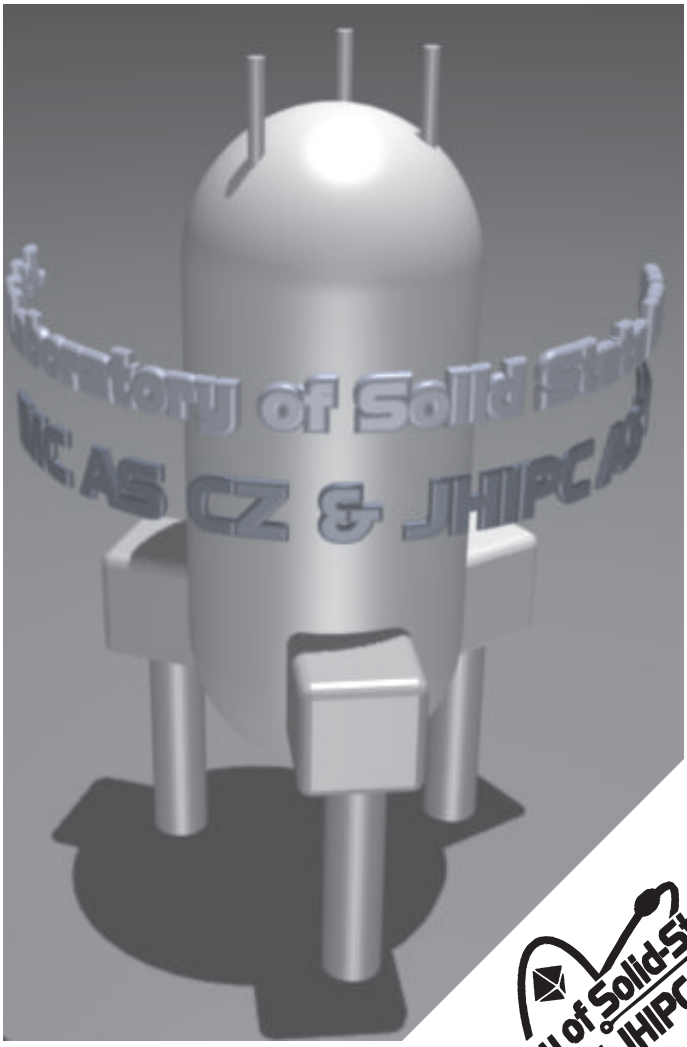

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