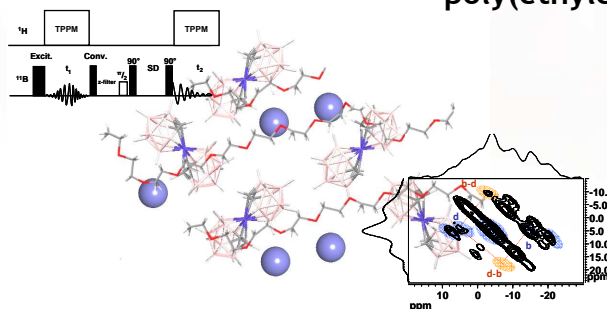


NMR krystalografie komplexu Na[3-cobalt(III) bis(1,2-dicarbollide)]- poly(ethylen oxid)



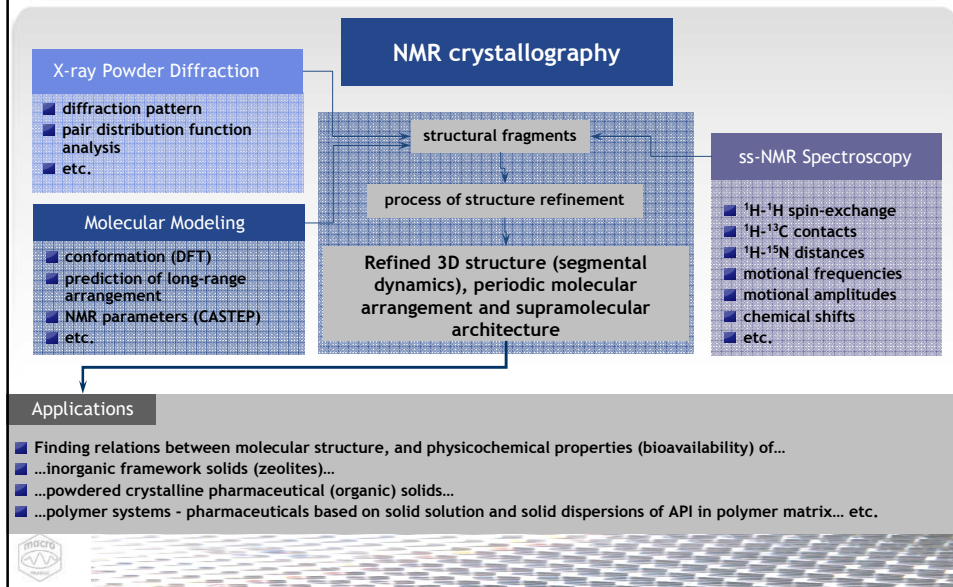
Přehled

- 1. Projekt I: NMR krystalografie metergolinu (44 x 5 x 20 A)
 - Test ^1H - ^{13}C HETCOR experimentů, ^{13}C - ^{13}C INADEQUATE
 - Rafinace struktury ss-NMR a XRPD
 - NMR-CASTEP výpočty

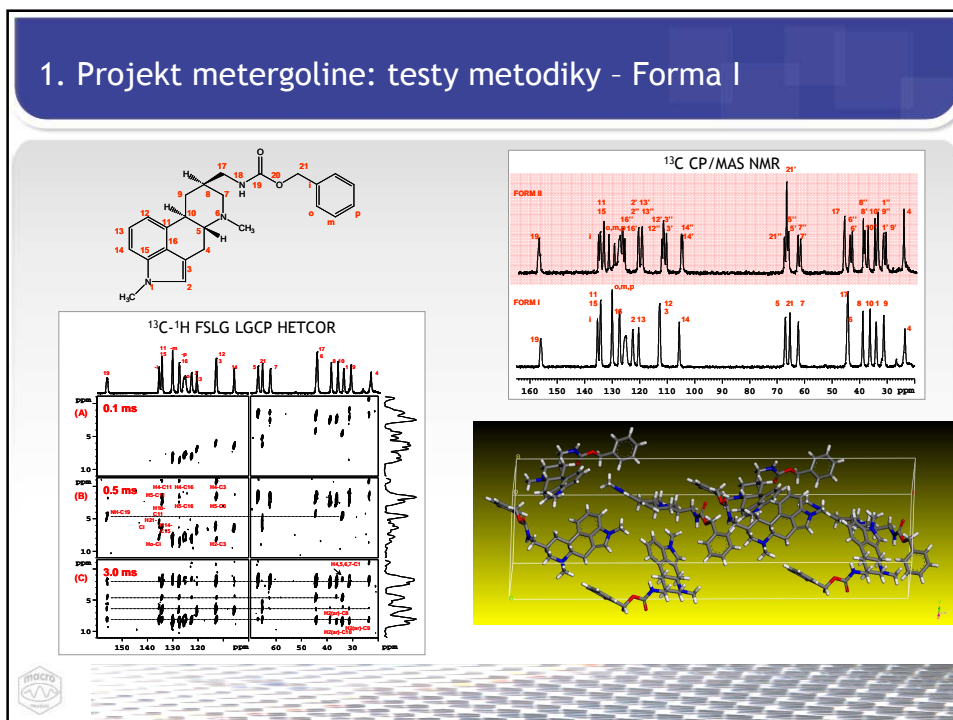
- 2. Projekt II: NMR krystalografie metallocarboran-PEO (12 x 14 x 17 A)
 - Příprava [Co bis(dicarbollide)-PEO] komplexu
 - Primární data: XRPD, ^{13}C CP/MAS NMR, ^{11}B , ^{23}Na MAS NMR
 - Segmentová dynamika: ^1H - ^{13}C LGCP a ^1H - ^{11}B VCT experimenty
 - Lokalizace NaCoD: ^1H - ^{13}C , ^{11}B , ^{23}Na HETCOR experiments
 - Počet krystalografických míst: ^{11}B (^{23}Na) MQ/MAS NMR
 - ^{11}B MQ/MAS NMR a ^{11}B - ^{11}B spin-exchange experimenty

 - Rafinace struktury ss-NMR a WAXS

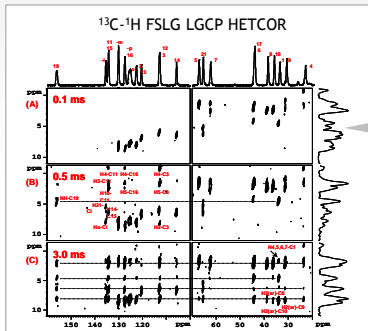
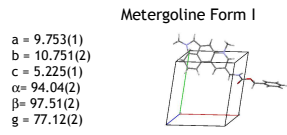
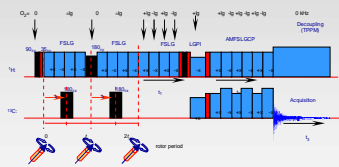
Základní experimentální koncept



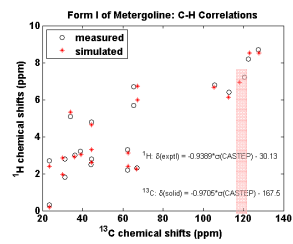
1. Projekt metergoline: testy metodiky - Forma I



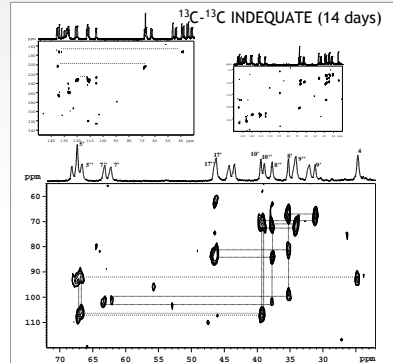
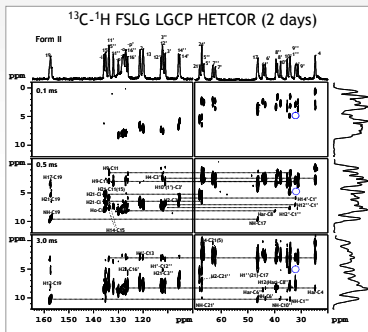
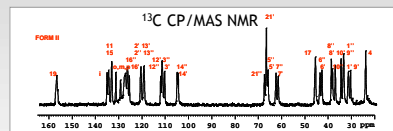
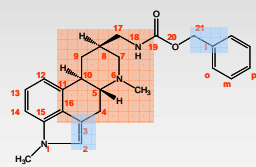
1. Projekt metergoline: CASTEP-NMR výpočty - Forma I



CASTEP-NMR vs. experimental ^1H and ^{13}C NMR shifts (RMSD 1.6 ppm in ^{13}C)

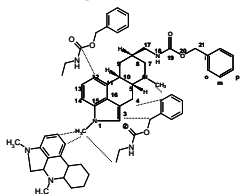


1. Projekt metergoline: „Neznámá“ Forma II



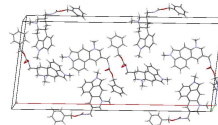
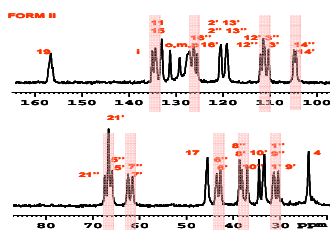
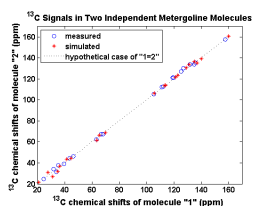
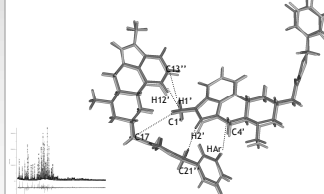
1. Projekt metergoline: Upřesnění struktury z neúplných dat

ss-NMR fragments (from HETCOR)



ss-NMR, XRPD
and CASTEP-NMR

Refined XRPD structure



a = 44.5784(7) α = 90
b = 4.86950(7) β = 99.2298(8)
c = 20.33592(33) γ = 90

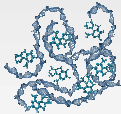


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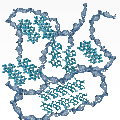
2. Projekt tuhé disperze polymer-léčivo

Alternative formulations

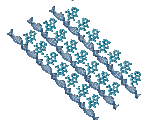
Solid solutions polymer-API
(amorphous-amorphous)



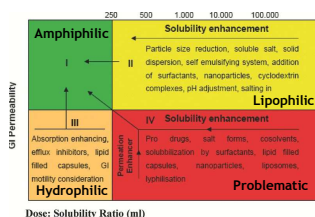
Solid dispersions polymer-API
(amorphous-crystalline)



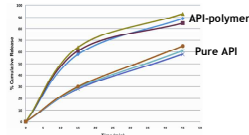
Polymer-API
co-crystals



Biopharmaceutical classification
system

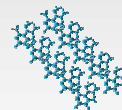


Dissolution profile

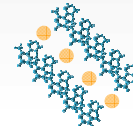


Traditional formulations

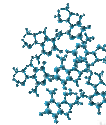
Pure crystal forms



Salts and co-crystals



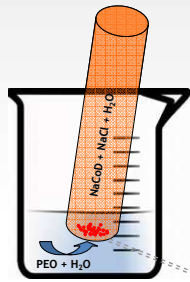
Amorphous forms



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2. Projekt tuhé disperze polymer-léčivo: příprava

Spontaneous precipitation of sodium [3-cobalt(III) bis(1,2-dicarbollide)], NaCoD, with poly-(ethylene oxide), PEO, in salted aqueous solutions.



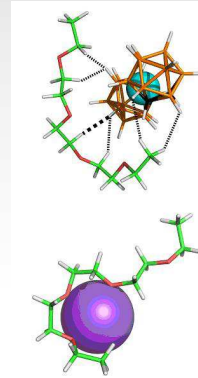
Solid solution of NaCoD in PEO

Factors leading to the formation of the complex NaCoD-PEO:

1. formation of dihydrogen bonds between negatively charged H-B atoms of CoD- clusters and slightly positively charged H atoms of PEO
2. Interaction between alkaline cations with oxygen atoms of PEO



Metallocrborane (NaCoD) - PEO

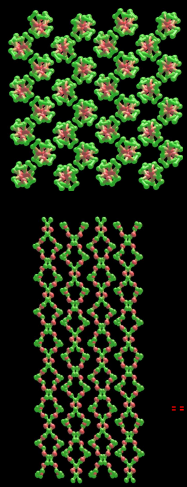


[3-cobalt(III) bis(1,2-dicarbollide)](-1)
NaCoD

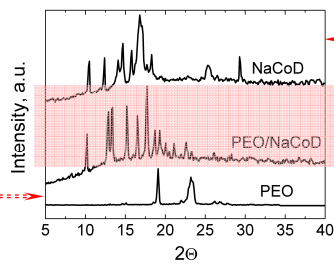
Matejicek Pavel; Zednik Jiri; Uselova Katerina; et al. *et al.*, Stimuli-Responsive Nanoparticles Based on Interaction of Metallocarborane with Poly(ethylene oxide), *Macromolecules* 42, 4829 (2009).

2. Projekt tuhé disperze polymer-léčivo: WAXS

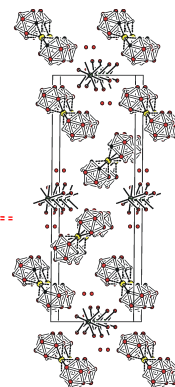
Crystal structure of PEO



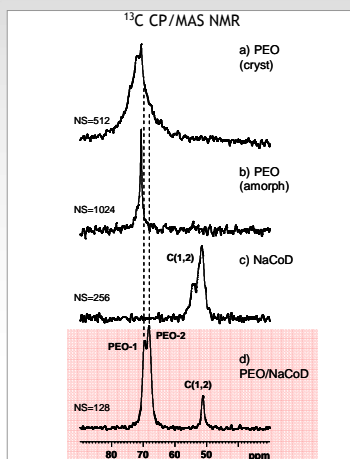
XRPD (WAXS) NaCoD-PEO komplexu



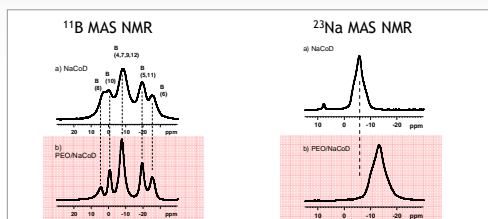
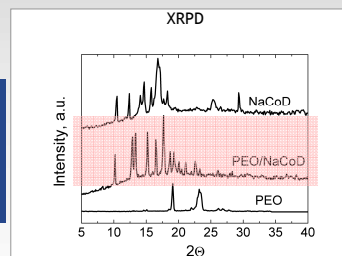
Crystal structure of NaCoD



2. Projekt tuhé disperze polymer-léčivo: ss-NMR

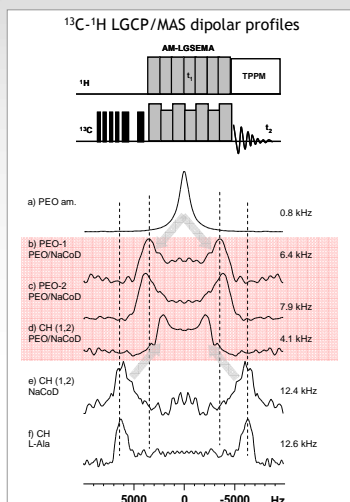


¹³C CP/MAS, ¹¹B, ²³Na... MAS NMR & XRPD



Broad ¹³C CP/MAS NMR signal of crystalline PEO as well as narrow signal of amorphous PEO disappeared; new signals of PEO appeared at low-frequency region; ¹³C CP/MAS and ¹¹B MAS NMR signals of CoD- significantly narrowed, while ²³Na MAS NMR signal is broadened and shifted to low-frequency region when forming PEO/NaCoD composite: PEO as well as NaCoD undergo mutual self-organization; changes in segmental dynamics can be expected.

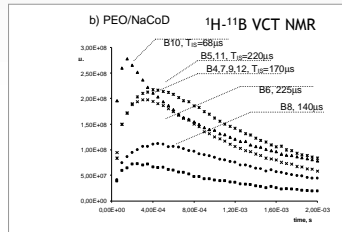
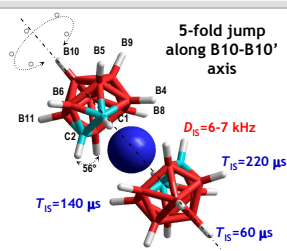
2. Projekt tuhé disperze polymer-léčivo: dynamika



Motional amplitudes (¹H-¹³C and ¹H-¹¹B dipolar data)

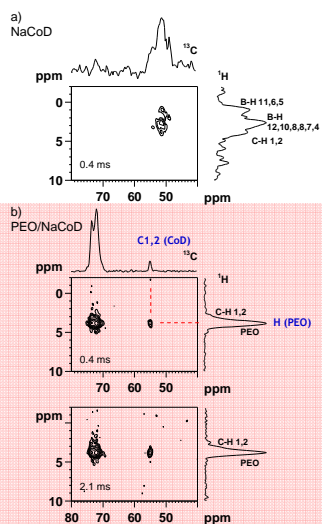
$$S^2 = 1 - \frac{3}{2} \langle \theta^2 \rangle$$

$$S^2 = \sum_{i,j=1}^N p_i p_j P_2(\cos \theta_{ij})$$

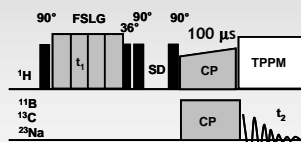


Significant increase in ¹H-¹³C dipolar couplings of PEO segments was detected in NaCoD/PEO complex, while the dipolar couplings of CH units of CoD-clusters dramatically decrease; ¹H-¹¹B cross-polarization rate constant is shortest for BH10 units on the top of both hemispheres: uniaxial rotation or 5-fold jump along B10-B10' axis is indicated.

2. Projekt tuhé disperze polymer-léčivo: domény? PEO



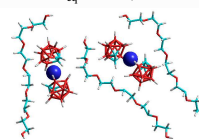
^1H - ^{13}C
heteronuclear
correlation FSLG
HETCOR with ^1H - ^1H
spin diffusion



$$D = \frac{\pi x^2}{4\epsilon^2 t_{\text{eq}}}$$

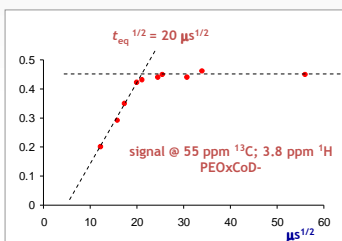
$$D = 0.3 - 0.5 \text{ nm}^2 \cdot \text{ms}^{-1}$$

$$t_{\text{eq}} = 400 \mu\text{s}$$

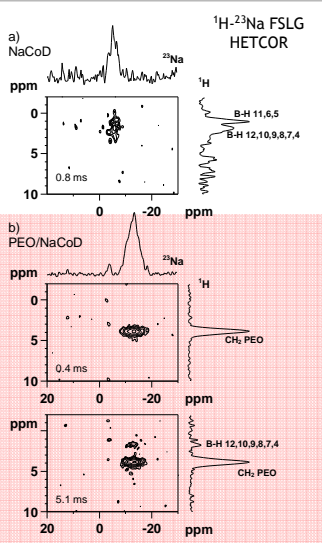


$$x = 0.4 - 0.5 \text{ nm}$$

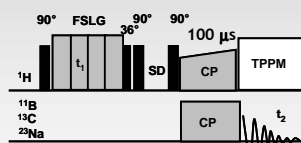
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2. Projekt tuhé disperze polymer-léčivo: lokalizace Na^+



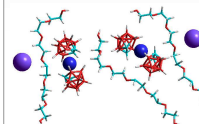
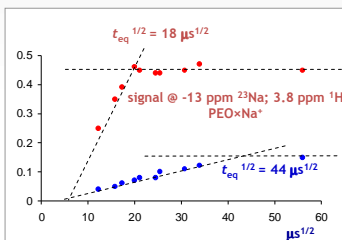
^1H - ^{23}Na
heteronuclear
correlation FSLG
HETCOR with ^1H - ^1H
spin diffusion



$$D = \frac{\pi x^2}{4\epsilon^2 t_{\text{eq}}}$$

$$D = 0.3 - 0.5 \text{ nm}^2 \cdot \text{ms}^{-1}$$

$$t_{\text{eq}} = 320 \mu\text{s} \quad t_{\text{eq}} = 2000 \mu\text{s}$$

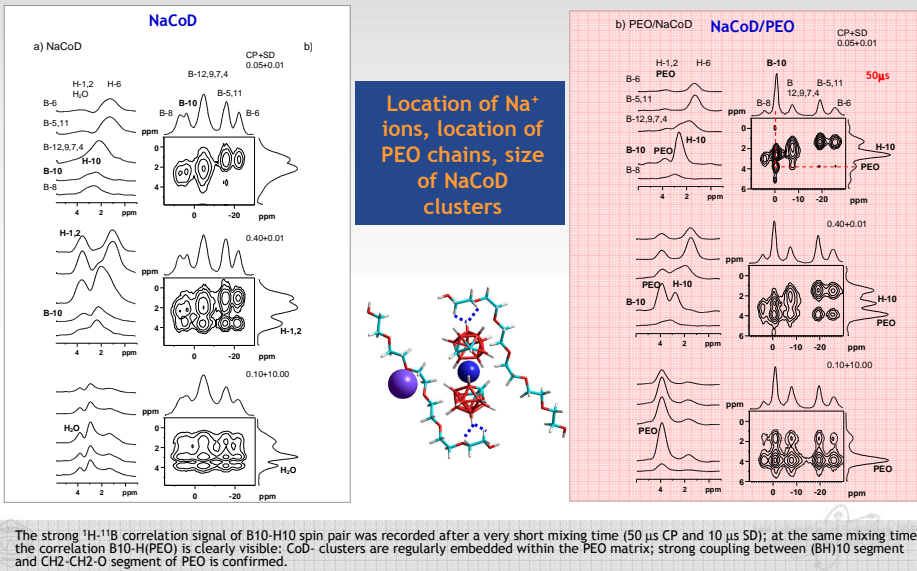


$$x = 0.4 \text{ nm}$$

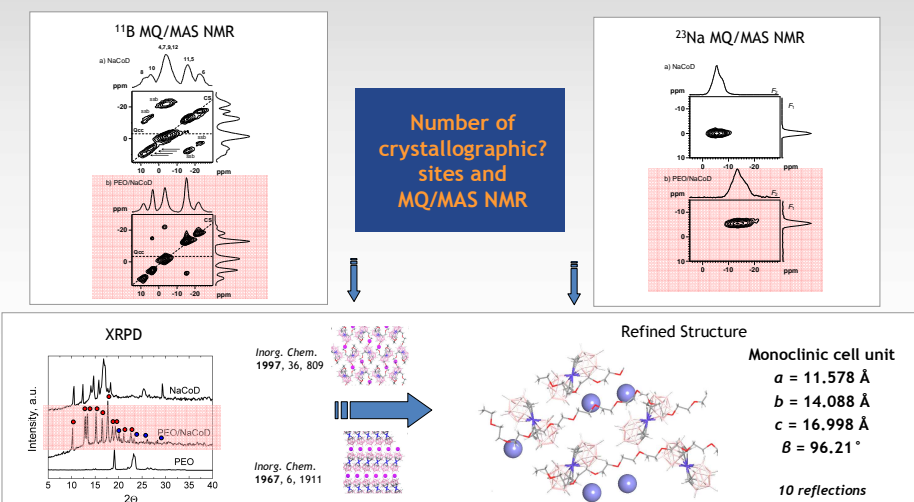
$$x = 1.1 \text{ nm}$$

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2. Projekt tuhé disperze polymer-léčivo: interakce PEO-NaCoD

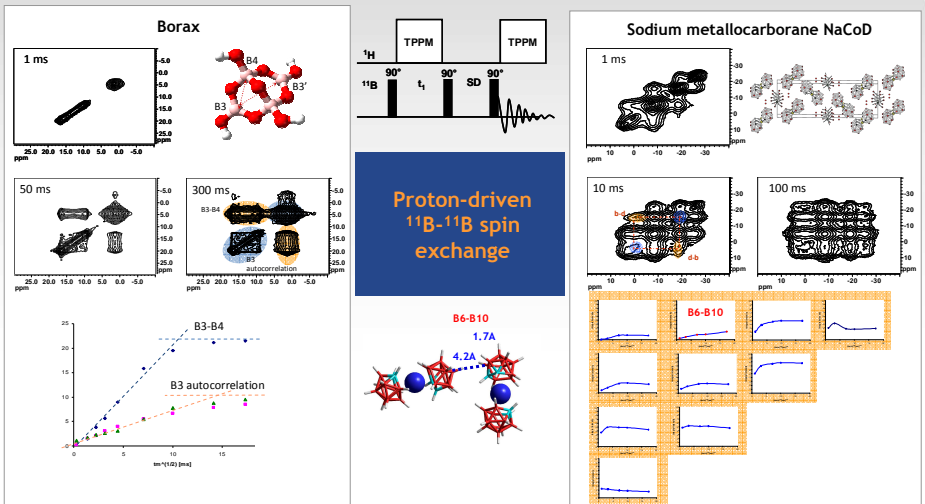


2. Projekt tuhé disperze polymer-léčivo: struktura z WAXS



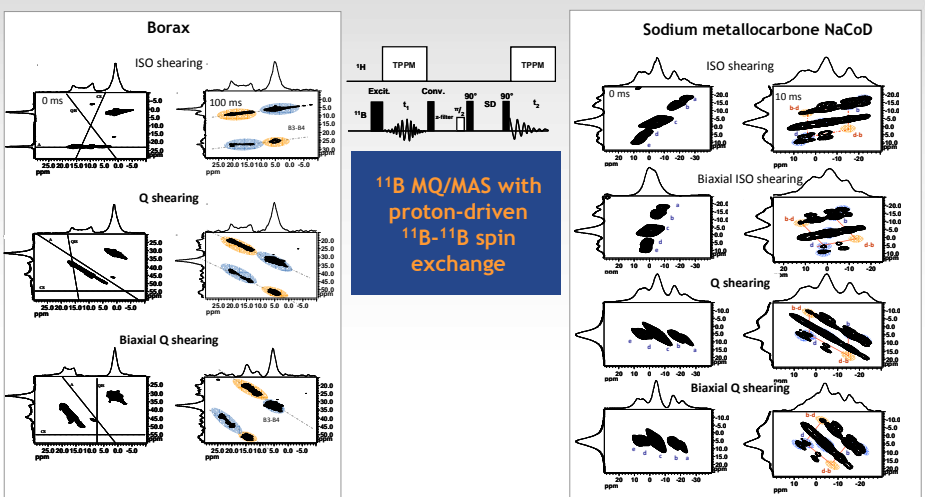
Pavel Matejcek, Jiri Brus *et al.* „On the Structure of Polymeric Composite of Metallacarborane with Poly(ethylene oxide), *Macromolecules* 44, 3847 (2011); DOI: 10.1021/ma200502t

Perspektivy ^{11}B NMR krystalografie?: ^{11}B - ^{11}B spinová výměna



- At 25 kHz in 3.2 mm probehead using a standard three-pulse sequence with ^1H decoupling during both evolution period the off-diagonal signals correlating non-equivalent ^{11}B atoms (2.5 Å) are fully developed after 100 ms. Autocorrelation signals evolve 300ms.
- Spin-exchange between directly bonded boron atoms is completed within 10-25 ms. In some case additional signal build-up was detected.

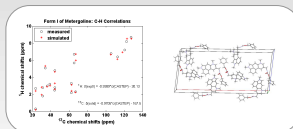
Perspektivy ^{11}B NMR krystalografie?: ^{11}B - ^{11}B MQ/MAS SD



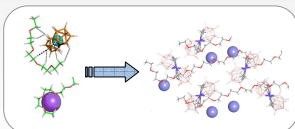
- Incorporating a spin-exchange period after the triple-quantum pulse sequence the resolution of the ^{11}B - ^{11}B correlation spectrum is enhanced. No autocorrelation signals evolve.
- The most suitable representation of MQ/MAS spin-exchange correlation experiments is provided by the recently developed biaxially sheared spectra. These spectra allow for a clear separation correlation signals.

Summary

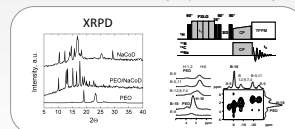
Upřesnění struktury z neúplných dat



[Co bis(dicarbollide)-PEO] complex

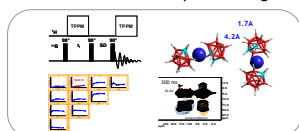


Global architecture of polymeric composite

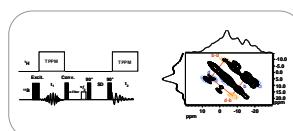


Solid-state NMR and polymers

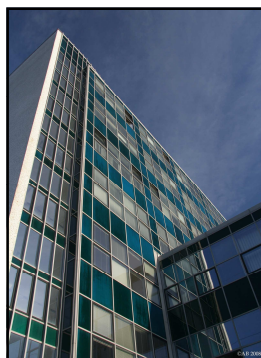
Proton-driven ^{11}B - ^{11}B spin exchange



^{11}B MQ/MAS with ^{11}B - ^{11}B PDSD



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



Alena Braunová, ©AG2008

Martina Urbanova
Libor Kobera
Olivia Policianova
Jiri Czernek
Josef Pleštil



Pavel Matějčiček



Charles University in Prague

Hana Brusova

ZENTIVA
part of the sanofi-aventis group



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