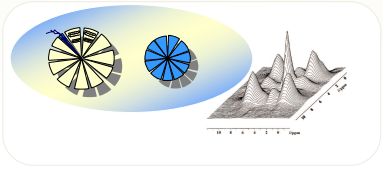
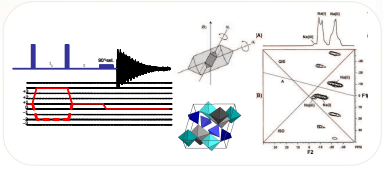
Joint Laboratory of Solid-State NMR
IMC AS CZ and JHIPC AS CZ

Author:
jiri brus

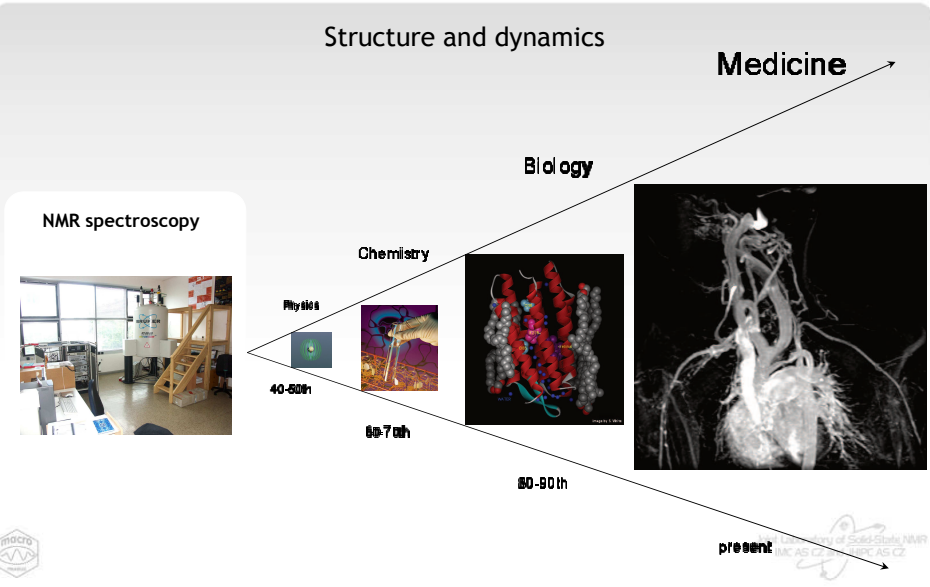
Institute of Macromolecular
Chemistry AS CR
Heyrovský Sqr. 2
162 06 Praha 6
Czech Republ.

Úvod do NMR spektroskopie: základní milníky





NMR spektroskopie ve fyzice, chemii, biologii atd…



Úsvit vesmíru a NMR

"Epoch of Nucleosynthesis" - 3 min - 400 000 years: 10^9-3000 K - formation of heavier nuclei

"Lepton Epoch" - 1s - 3 min: 10^{10}-10^9K - formation of protons

"Hadron Epoch" - 10^{-6}-1s: 10^{13}-10^{10}K - quarks combine to form protons and neutrons

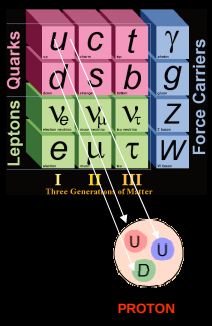
"Electroweak Epoch" - 10^{-12}-10^{-6} s: 10^{15}-10^{13}K - formation of electrons and pozitrons

"Grand Unification Epoch" - 10^{-35}-10^{-12} s: 10^{27}-10^{15}K - formation of quarks

"Planck Epoch" - 10^{-43}-10^{-345}s: 10^{32}-10^{27}K

time

The Big Bang -time 0 s



PROTON

α - 1/137

Spin predicted by W. Pauli in 1924 as the 4-th quantum number

1945 - Nobel Prize

Historie – měření magnetického momentu 1938

RADAR technologie

Isidor Isaac Rabi
1898-1988
1944 - Nobel Prize

$E = h.\nu = 6{,}6262 \cdot 10^{-34} \times 5 \cdot 10^{8} = 3{,}31 \cdot 10^{-25}$ J

0,001g hmoty .....$2 \cdot 10^{-4}$ J

$E = mc^2$.... v 0,001g hmoty se ukrývá $9 \cdot 10^{10}$ J

Rabi II, Zacharias JR, Millman S, Kusch P.
A new method of measuring nuclear magnetic moment.
Phys Rev 1938; 53: 318.

The Molecular Beam Resonance Method for Measuring Nuclear Magnetic Moments

The Magnetic Moments of Li^6, Li^7 and F^{19}

I. I. Rabi, S. Millman, P. Kusch, Columbia University, New York, New York

and

J. R. Zacharias, Hunter College, New York, New York

(Received January 30, 1938)

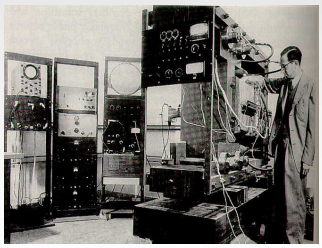
Historie – první NMR signály 1946-51

Felix Bloch
1905-1983

Edward M. Purcell
1912-1997

1952 – Nobel Prize

Laboratoř F. Blocha



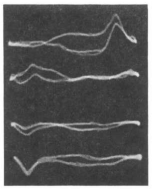
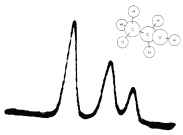
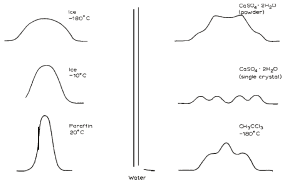


FIG. 10. Photographic record of the proton signal in water. The four traces from top to bottom correspond to the times t_1, t_2, t_3, t_4 of Fig. 9. In the text they are referred to as a, b, c, d, respectively.

Bloch, F.; Hansen, W. W.; Packard, M.
The nuclear induction experiment
Physical Review (1946), 70 474-85.



Arnold, J.T., S.S. Dharmatti, and M.E. Packard,
J. Chem. Phys., 1951. 19: p. 507.



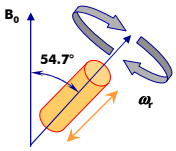
Historie – rotace vzorku pod magickým úhlem 1958

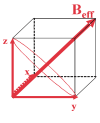
I.J. Lowe

Lowe, I.J.
Free Induction Decays in Rotating Solids, *Phys. Rev. Lett.* (1959); 2: 285.

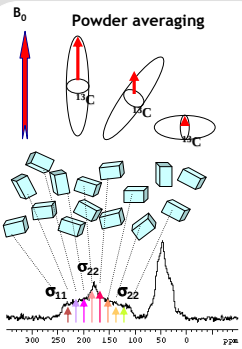
Andrew E.R., Bradbury A., Eadges R.G.
NMR spectra from a Crystal Rotated at High Speed, *Nature* (1958); *182*: 1659.

Magic angle spinning

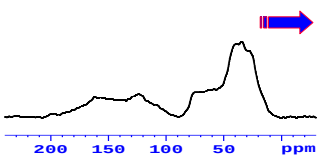




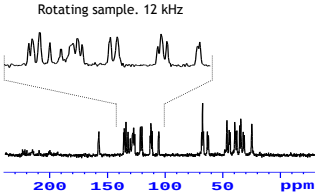
Powder averaging



Static sample



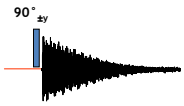
Rotating sample. 12 kHz



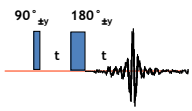
Historie – Hahnovy experimenty (1950-1962)

Erwin. L. Hahn
*1921

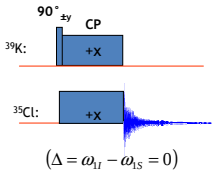
FID



Spin echo

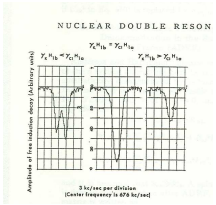


Cross polarization



$$(\Delta = \omega_{1I} - \omega_{1S} = 0)$$

$$\gamma_K B_{1K} = \gamma_{Cl} B_{1Cl}$$



Hahn, E. L.,
Spin echoes, *Phys. Rev.*, *80*, 580-594 (1950).

Hahn, E. L.,
Free nuclear induction, *Physics Today*, Nov. (1953), pp. 4-9.

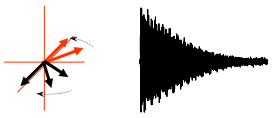
Hartmann S.R., Hahn E.L.
Nuclear Double Resonance in Rotating Frame, *Phys. Rev.* (1962); *128*: 2042.

Historie – Pulsní NMR (1966…….1822)

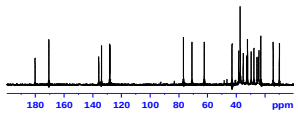
Richard R. Ernst
*1933
1991 - Nobel Prize

Ernst R.R., Anderson W.A.
Application of FT Spectroscopy to Magnetic resonance, *Rev.Sci.Instr. (1966); 37: 93.*

Free Induction Decay
FID



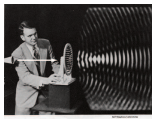
Spectrum



Jean Baptiste Joseph
Fourier

1768-1830

Noise waves



$$F(\omega) = \int_{-\infty}^{\infty} dt.\, f(t) e^{-i\omega t}$$

Sheet of music

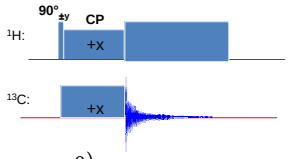
Fourier J.B.J.
Theorie analytique da la chaleur, *Firmin Didot, pere et fils, Paris. (1822).*

Křížová-polarizace – 1972

Zvýšení citlivosti NMR experimentu

Alex Pines
*1945

Pines A., Gibby M.G., Waugh J.S.
Proton-Enhanced Nuclear Induction Spectroscopy. A Method for High Resolution NMR of Dilute Spins in Solids, *J. Chem. Phys.* (1972); *56*: 1776.



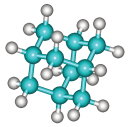
$$(\Delta = \omega_{1I} - \omega_{1S} = 0)$$

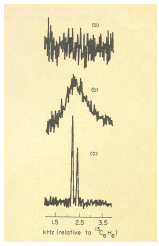
$$\gamma_H B_{1H} = \gamma_C B_{1C}$$

Zvýšení citlivosti až 1000-krát

1) **Polarizace izotopicky hojných jader *I*.**
2) **Snížení spinové teploty jader *I* v rotující soustavě souřadné.**
3) **Ustavení kontaktu mezi *I* a *S* - spin-lock a HH kontakt.**
4) **Detekce magnetizace *S* při současném dekaplinku *I*.**

Adamantan



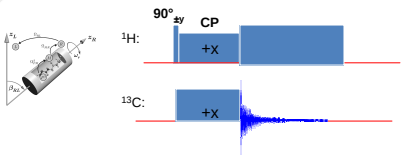


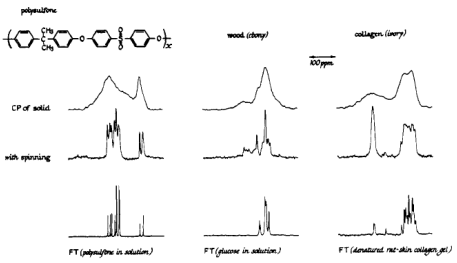
Křížová-polarizace – 1976

Zvýšení citlivosti NMR experimentu

J. Schaefer

Schaefer J., Stejskal E.O.J.
¹³C NMR of Polymers Spinning at Magic Angle, *J. Am. Chem. Soc.* (1976); *98*: 1031.





Zvýšení citlivosti až 1000-krát

1) **Polarizace izotopicky hojných jader *I*.**
2) **Snížení spinové teploty jader *I* v rotující soustavě souřadné.**
3) **Ustavení kontaktu mezi *I* a *S* - spin-lock a HH kontakt.**
4) **Detekce magnetizace *S* při současném dekaplinku *I*.**

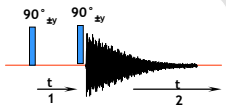
Objev více-rozměrné NMR spektroskopie (1971)

Jean Luis Charles Jeener
*1931

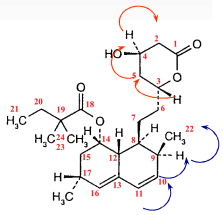
Přenos magnetizace přes vazebné elektrony (konektivita řetězce)

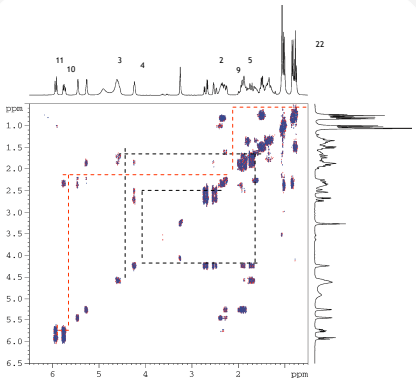
Přednáška na letní škole v Basko Polje, Jugoslávie, 1971
Dvoudimenzionální NMR, COSY

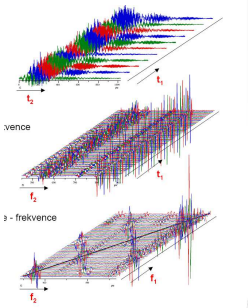
Aue W.P., Bartholdi E., Ernst R.R.
2D Spectroscopy. Application to NMR, *J. Chem. Phys.* (1976); *64*: 229.



2D COSY NMR





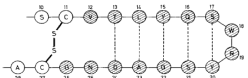


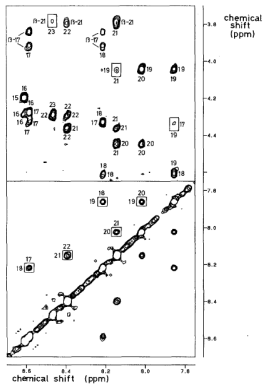
Historie – 3D struktura proteinů (1986)

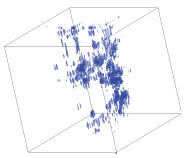
Allen D. Kline, Werner Braun and Kurt Wüthrich,

Studies by 1H nuclear magnetic resonance and distance geometry of the solution conformation of the α-amylase inhibitor Tendamistat. *J MOL BIOL* 189 (2): 377-382 MAY 20 1986

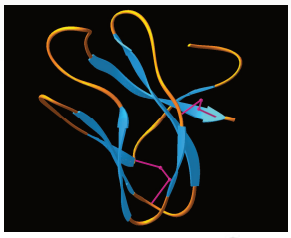
Kurt Wüthrich
*1938
2002 – Nobel Prize







TENDEMISTAT



Historie – 3D struktura proteinů (2006)

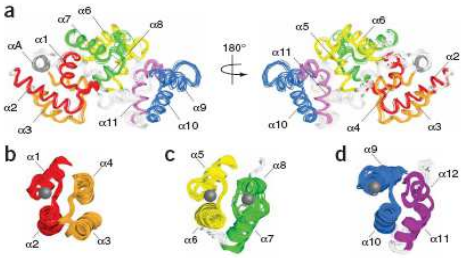
Calbindin-D28K - inhibits caspase-3, that induces formation of amyloid plaks.

John Canavagh
*1960

Kojetin DJ, Venters RA, Kordys DR, Thompson RJ, & Kumar R & Cavanagh J., Structure, binding interface and hydrophobic transitions of Ca2+-loaded calbindin-D28K. *NSMB (2006) 13, : 641-647*

"If you don't know the shape of the protein, you can't figure out how it works," Cavanagh says. "It took a long time, about five years, but we've characterized the structure of this protein and found where it binds caspase-3. Insight into how it binds to caspase-3 might lead to a way of exploiting those interactions to develop therapeutics."

Calbindin-D28K

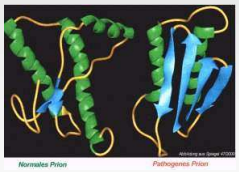


Prionová onemocnění mozku

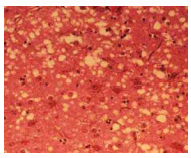
František Koukolík
*1954

Neuropatolog, primář patologie Fakultní Thomayerovy nemocnice v Praze a vedoucí Národní referenční laboratoře TSE/CJN

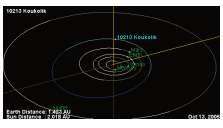
Konformační polymorfismus proteinů



Zdravý PrPC *Poškozený PrPSc*



Bublinky vzniklé v nemocné mozkové tkáni



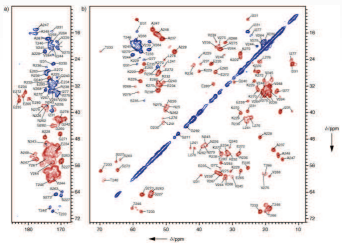
3D struktura prionových proteinů (2005)

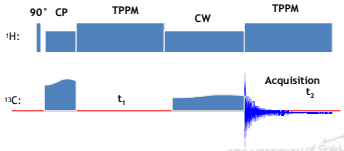
Beat.H. Meier
*1954

Meier B.H. et al.,
Correlation of Structural Elements and Infectivity of the HET-s prion, *Nature* (2005); *435(9)*: 844.

PrPC PrPSc

2D ^{13}C-^{13}C DREAM NMR

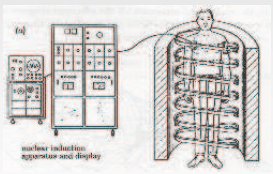




Zobrazování magnetickou rezonancí

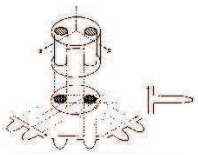
Středem zájmu je voda

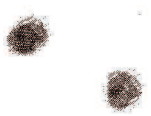
Raymond Damadian (1971)



Postupný řez hlavou

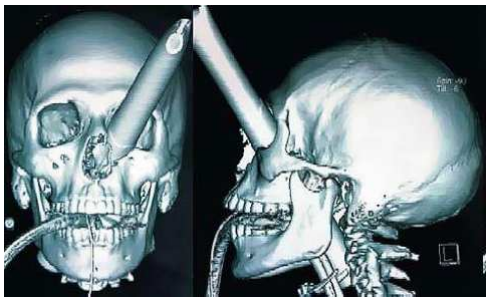
Paul Lauterbur (1973)





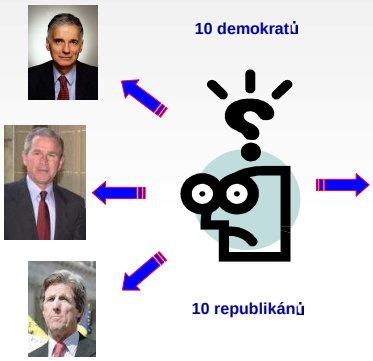
Zobrazování magnetickou rezonancí

Zázrak nebo podvrh

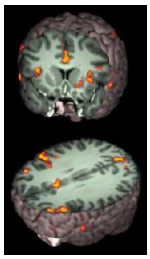


Funkční NMR

Jonas T. Kaplan , Joshua Freedman and Marco Iacoboni,
Us versus them: Political attitudes and party affiliation influence neural response to faces of presidential candidates,
Neuropsychologia (2006)



Aktivace části mozku zvýší průtok krve. Potřeba kyslíku se projeví vyšším obsahem oxyhemoglobinu a poklesem deoxyhemoglobinu (paramagnetický). Aktivovaná místa mají silnější signál - svítí více než místa deaktivovaná. Nárůst intenzity je ale jen 1-5 %.



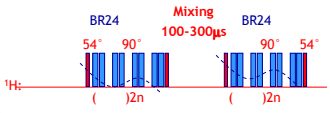
It might be suggested that personal opinions about these individual politicians rather than their actual political persuasion might also influence activity in the brain. However, it is probably best to keep out of any political office that has its own MRI machine, especially if you're not one of us.

2D korelační NMR v pevné fázi – 1985

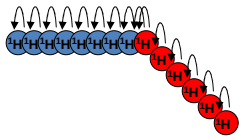
Morfologie polymerních směsí

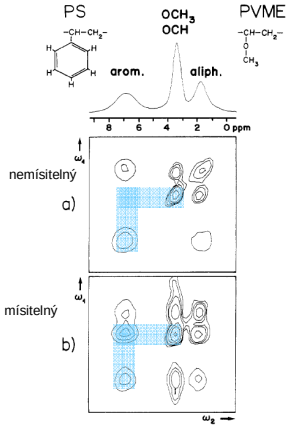
Caravatti P., Neuenschwander P., Ernst R.R.
Characterization of Heterogeneous Polymer Blends by 2D 1H Spin Diffusion Spectroscopy,
***Macromolecules*. (1985); *18*: 119.**

2D ^{1}H MAS NMR pulse sequence



Štafetový přenos polarizace
Korelace ^{1}H-^{1}H chemických posunů

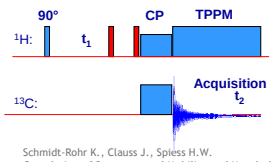




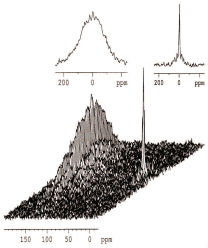
Dipolární separační experimenty (1987 - 1995)

Hans W. Spiess
*1933

2D ^{1}H-^{13}C WISE

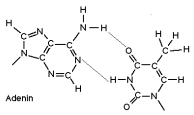


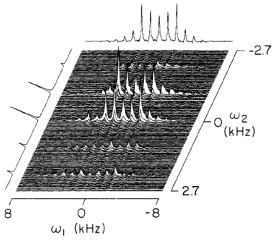
Schmidt-Rohr K., Clauss J., Spiess H.W.
Correlation of Structure and Mobility and Morphology by 2D Wideline-Separation NMR, *Macromolecules*. *(1992); 25: 3273.*



RG Griffin

2D ^{1}H-^{15}N SLF NMR





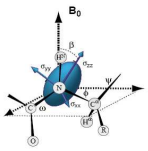
Griffin R.G.
Measurement of Heteronuclear Bond Distances in Polycrystalline Solids by Solid-State NMR, *J.Am.Chem.Soc. (1987); 109: 4163.*

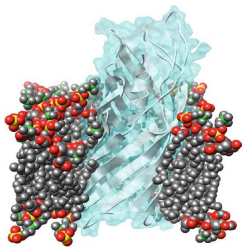
Orientované systémy (1995 – 2000)

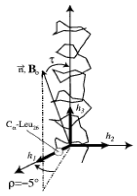
Strukturní biologie a membránové proteiny

Opella S.J.

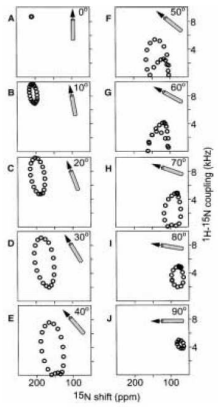
Wu C.H., Ramamoorthy A.,Opella S.J., **High Resolution Dipolar Solid-State NMR,** ***J.Magn.Reson. A*** **(1994);** ***109*****: 270.**







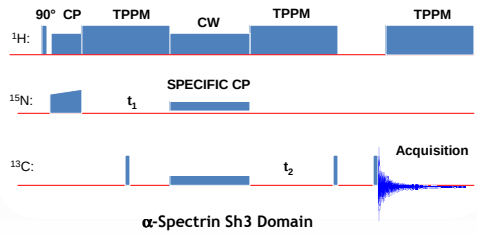
PISEMA:
Polarization Inversion Spin Exchange at Magic Angle



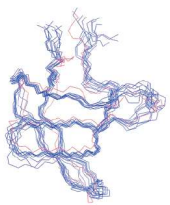
Mikrokrystalické proteiny – 2002

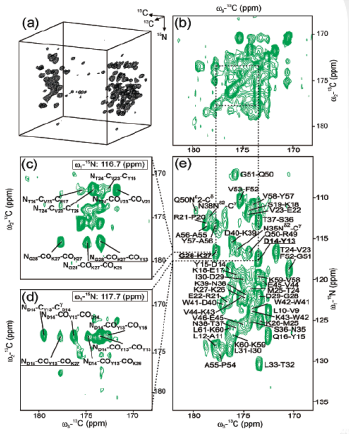
Experimenty s dvojitou cross-polarizací

Castellani, F., van Rossum, B.J., Diehl, A., Schubert, M., Rehbein, K., and Oschkinat, H. **Structure of a protein determined by solid-state magic-angle-spinning NMR spectroscopy,** ***Nature*** **420, 98-102 (2002).**



α-Spectrin Sh3 Domain





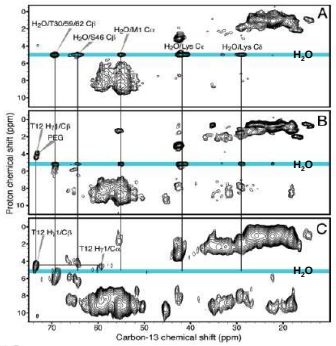
Mikrokrystalické proteiny – 2005-2006

Lokalizace vody - detekce ^{1}H NMR signálu

A. Böckmann, M. Juy, E. Bettler, L. Emsley, A. Galinier, F. Penin, A. Lesage, **Water-Protein Hydrogen Exchange in the Micro-Crystalline Protein Crh as Observed by Solid State NMR Spectroscopy,** ***Journal of Biomolecular NMR*** **, 32 195 (2005).**

Anne Lesage,Lyndon Emsley,Francois Penin,and Anja Bockmann, **Investigation of Dipolar-Mediated Water-Protein Interactions in Microcrystalline Crh by Solid-State NMR Spectroscopy,** ***J Am Chem Soc*** **128, 8246 (2006).**

2D ^{1}H-^{13}C HETCOR – mikrokrystalický systém

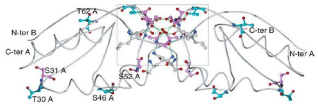


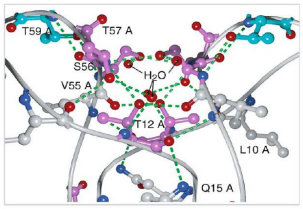
Detekce imobilizovaných i pohyblivých molekul (rezidenční čas – jednotky ns)

Přímá chemická výměna H2O-OH

Detekce zcela imobilizovaných a fixovaných molekul (rezidenční čas – jednotky µs)

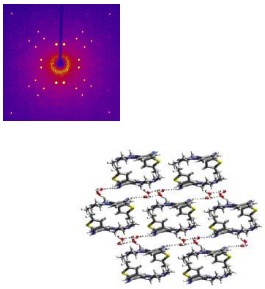
Mikrokrystalický protein Crh
(catabolite repression histidine containing phsphocarrier protein)





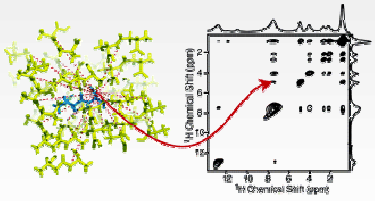
NMR krystalografie – 2006…

XRD



Reutzel-Edens S. et al. ***Crystal Growth & Design 3, 897 (2003)***

ss-NMR

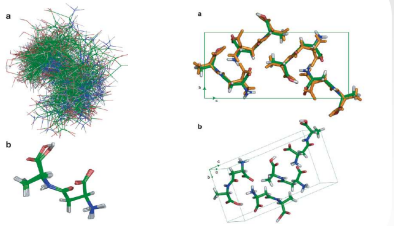


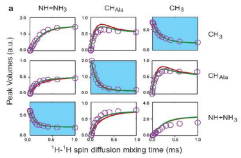
Elena B. et al. ***J. Am. Chem. Soc.*** **(2006);** ***128, 9555.***

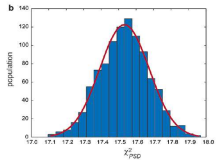
NMR krystalografie – 2006…

Elena B. et al.
Solid-state 1H NMR crystallography, *J. Am. Chem. Soc.* (2005); *127(25)*, 9140.

Elena B. et al.
Molecular Structure Determination in Powders by NMR Crystallography from Proton Spin Diffusion, *J. Am. Chem. Soc.* (2006); *128*, *9555*.







$$\frac{d\mathbf{M}}{dt} = -\mathbf{K}(\mathbf{M}-\mathbf{M}_0) \quad k_{ij} = \sum_{\lambda}\left(\frac{\mu_0\gamma^2\hbar}{4\pi}\right)^2 \frac{A}{(r_{ij}^n)_{\lambda}} \quad k_{ii} = -\sum_i k_a$$

$$\mathbf{M}(t,\tau_{SD}) = \exp(-\mathbf{K}\tau_{SD})\mathbf{M}_z(t,0) \qquad \mathbf{P}(\tau_{SD}) = \exp(-\mathbf{K}\tau_{SD})\mathbf{M}_z^a$$

n … *Functional dependence on internuclear distance*

$$\chi^2 = \sum \frac{(calc_i - t_i)^2}{\sigma_i^2}$$

NMR krystalografie

NMR crystallography

X-ray Powder Diffraction
- diffraction pattern
- pair distribution function analysis
- etc.

Molecular Modeling
- conformation (DFT)
- prediction of long-range arrangement
- NMR parameters (CASTEP)
- etc.

structural fragments

process of structure refinement

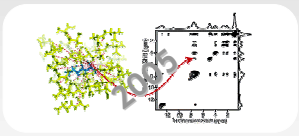
Refined 3D structure (segmental dynamics), periodic molecular arrangement and supramolecular architecture

ss-NMR Spectroscopy
- ^1H-^1H spin-exchange
- ^1H-^{13}C contacts
- ^1H-^{15}N distances
- motional frequencies
- motional amplitudes
- chemical shifts
- etc.

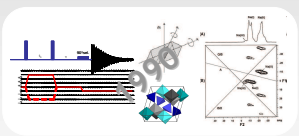
Applications
- Finding relations between molecular structure, and physicochemical properties (bioavailability) of…
- …inorganic framework solids (zeolites)…
- …powdered crystalline pharmaceutical (organic) solids…
- …polymer systems - pharmaceuticals based on solid solution and solid dispersions of API in polymer matrix… etc.

Souhrn

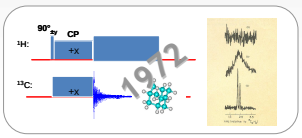
NMR krystalografie



MQ/MAS NMR – anorganické systémy

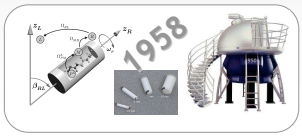


Cross-polarizace

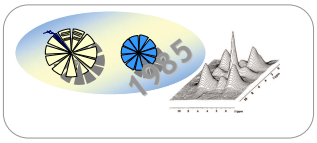


Solid-state NMR and .....

MAS – rotace vzorku pod magickým úhlem



Spinová difuse a morfologie polymerů



Struktura proteinů