NMR crystallography

I) Utilization of dipolar couplings for structure refinement
II) Polymorphism and segmental dynamics

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

Jiri Brus

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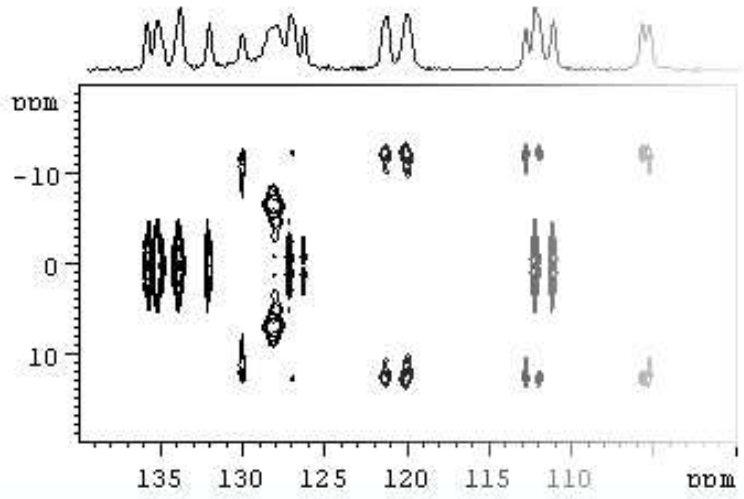
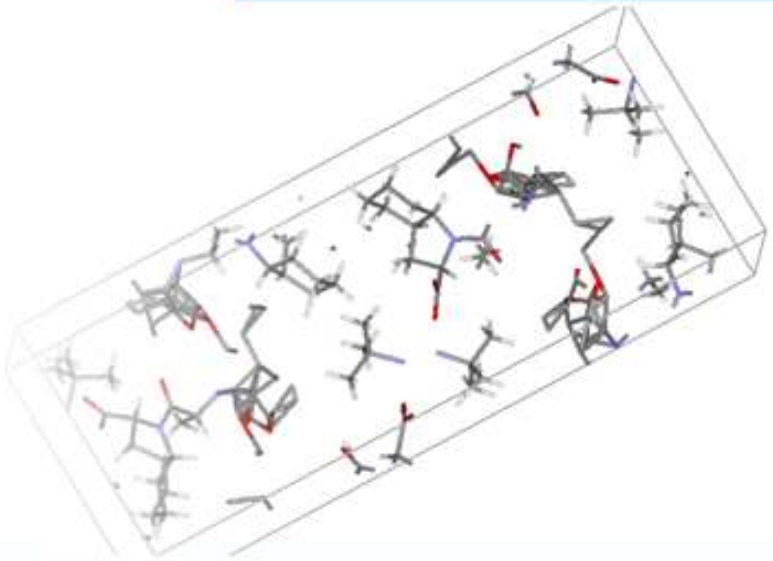
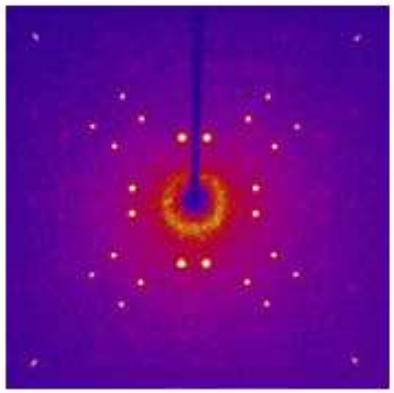




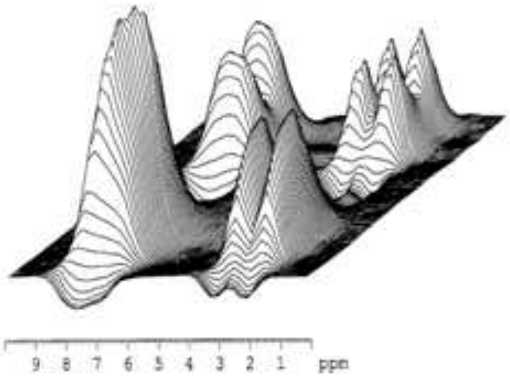
Solid-state NMR spectroscopy

NMR crystallography
(utilization of ^{1}H dipolar couplings)

XRD



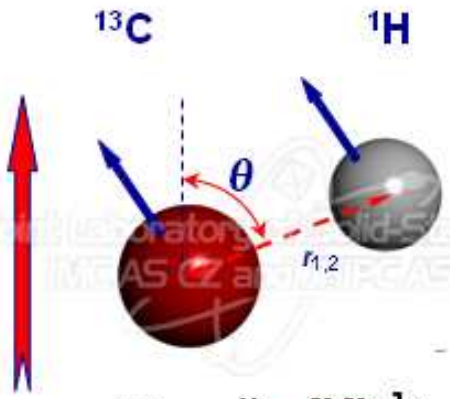
NMR



I) New crystal forms of simvastatin
II) New crystal form of metergoline – structural fragments and segmental dynamics
III) Dynamic disorder and crystal stability

NMR crystallography

Dipolar couplings and interatomic distances

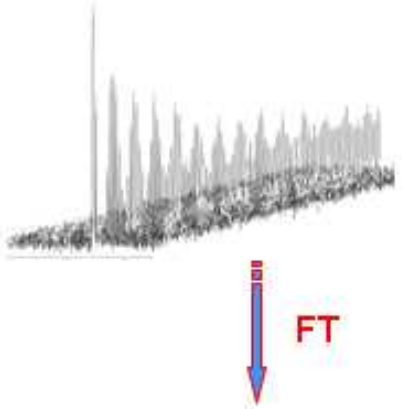


$$\hat{H}_D^{IS} = -\frac{\mu_0}{4\pi}\hbar\frac{\gamma_I\gamma_S}{r_{I,S}^3}\frac{1}{2}\left(3\cos^2\theta - 1\right)2\hat{I}_z\hat{S}_z$$

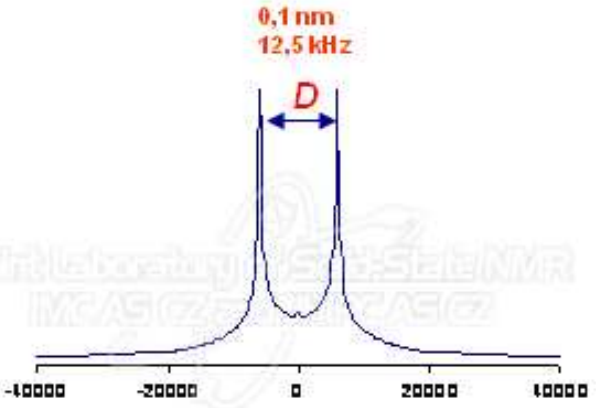
D – dipolar coupling constant depends on $1/r_{CH}^3$.

D – dipolar coupling constant should be the same for all C-H pairs in CH or CH_2 groups as bond length is always ca. 0.11 nm.

Dipolar oscillation of ^{13}C NMR signal



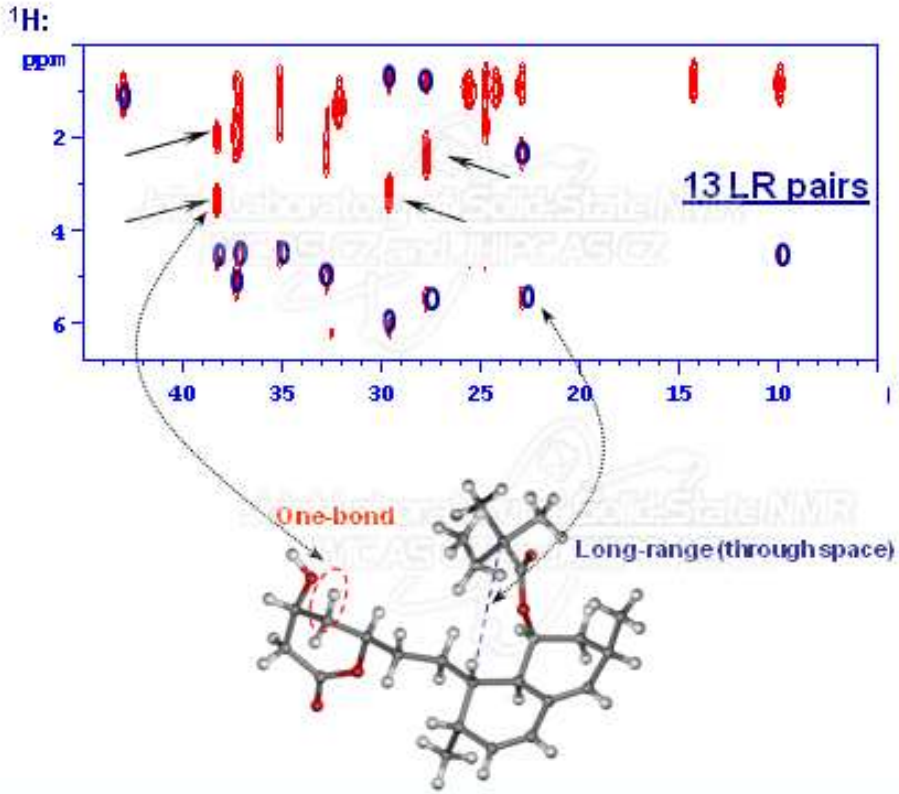
Dipolar spectrum

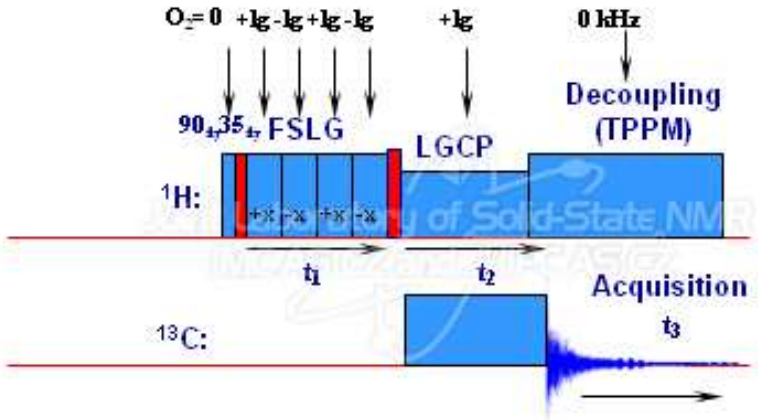


NMR crystallography

Dipolar couplings and interatomic distances
Basic experimental approach

Standard 2D experiment
^{1}H-^{13}C FSLG-LGCP-HETCOR



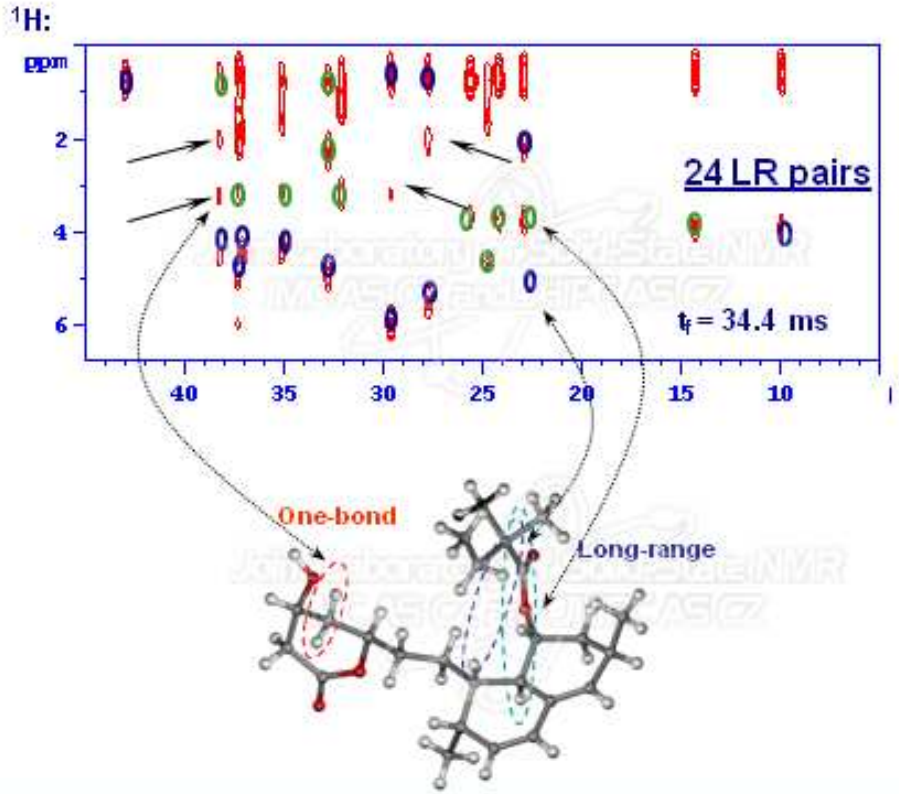


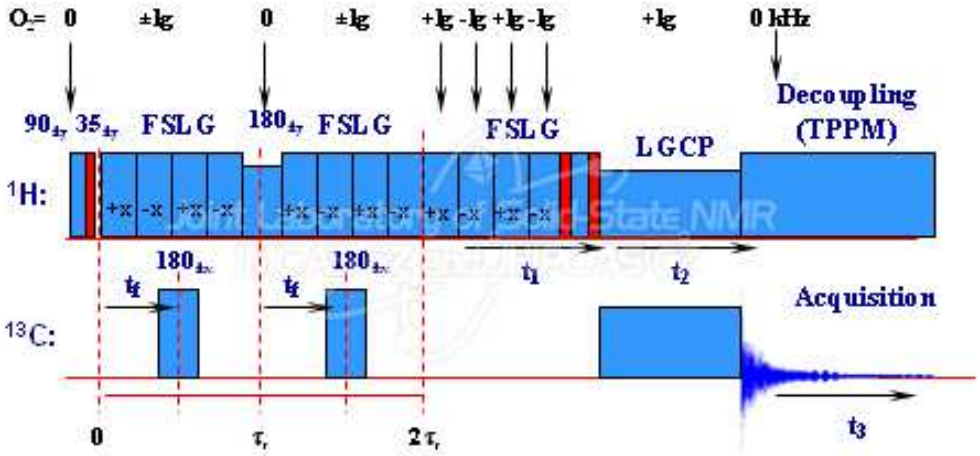
B.-J. van Rossum, et al. **J. Am. Chem. Soc. 122, 3465 (2000)**

NMR crystallography

Dipolar couplings and interatomic distances
Basic experimental approach

Extended 2D experiment
REDOR dephased
^{1}H-^{13}C FSLG-LGCP-HETCOR





Yao X.L., *et al.* **J. Magn. Reson. *149*, 139 (2001)**

NMR crystallography

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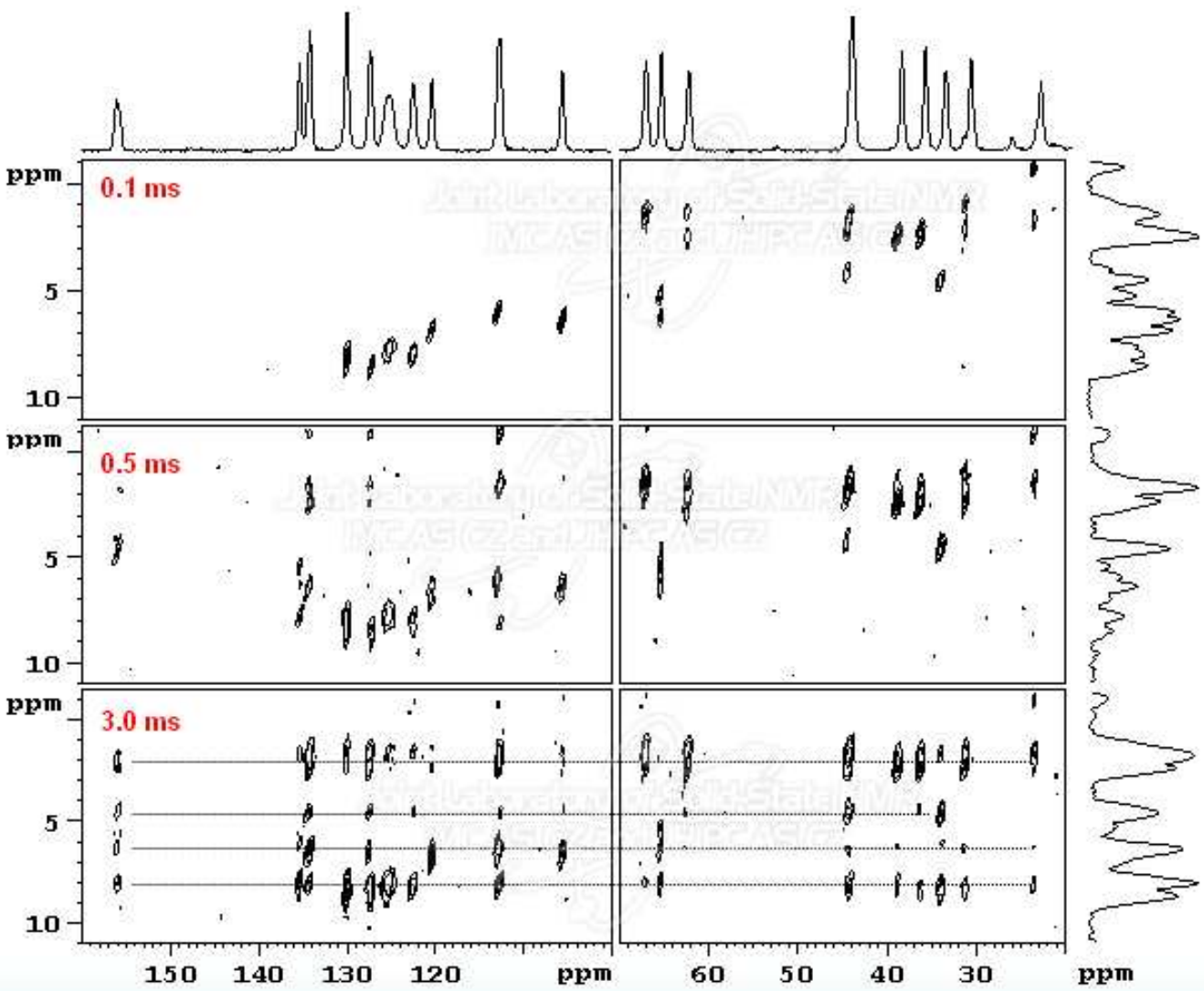
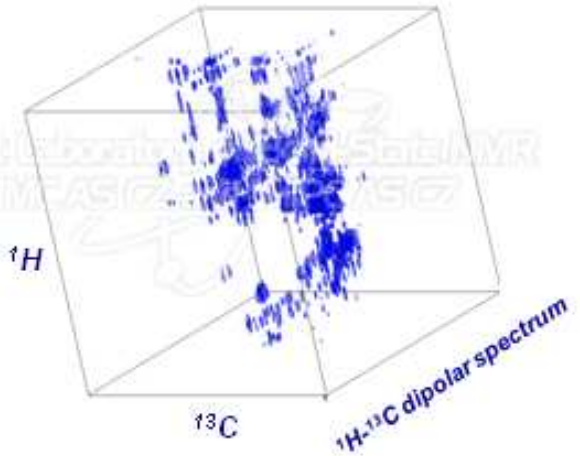
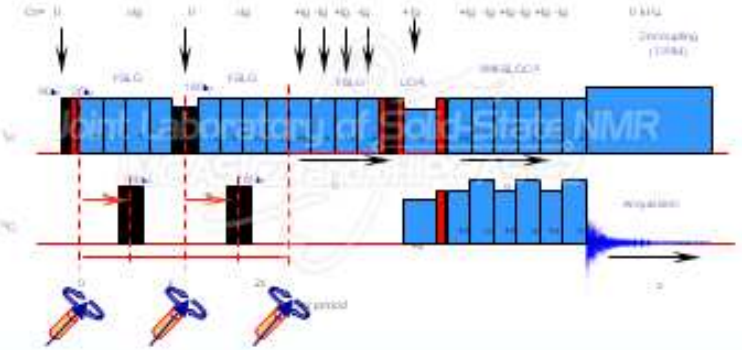
Dipolar couplings and interatomic distances
Basic experimental approach



"3D" experiment





New low-temperature polymorphs of simvastatin

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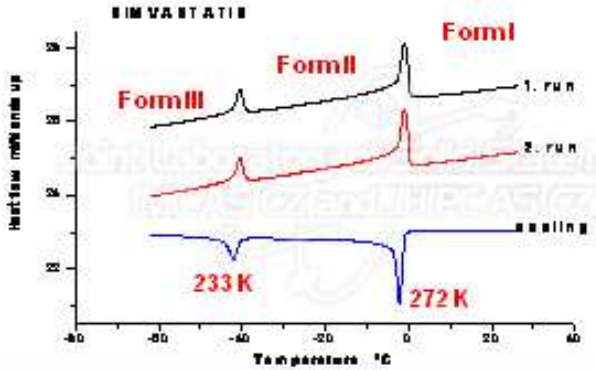
DSC measurement

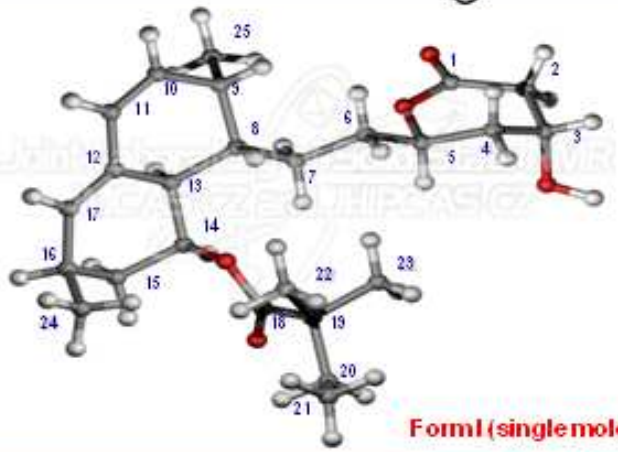


Simvastatin (Zocor®)

Merck

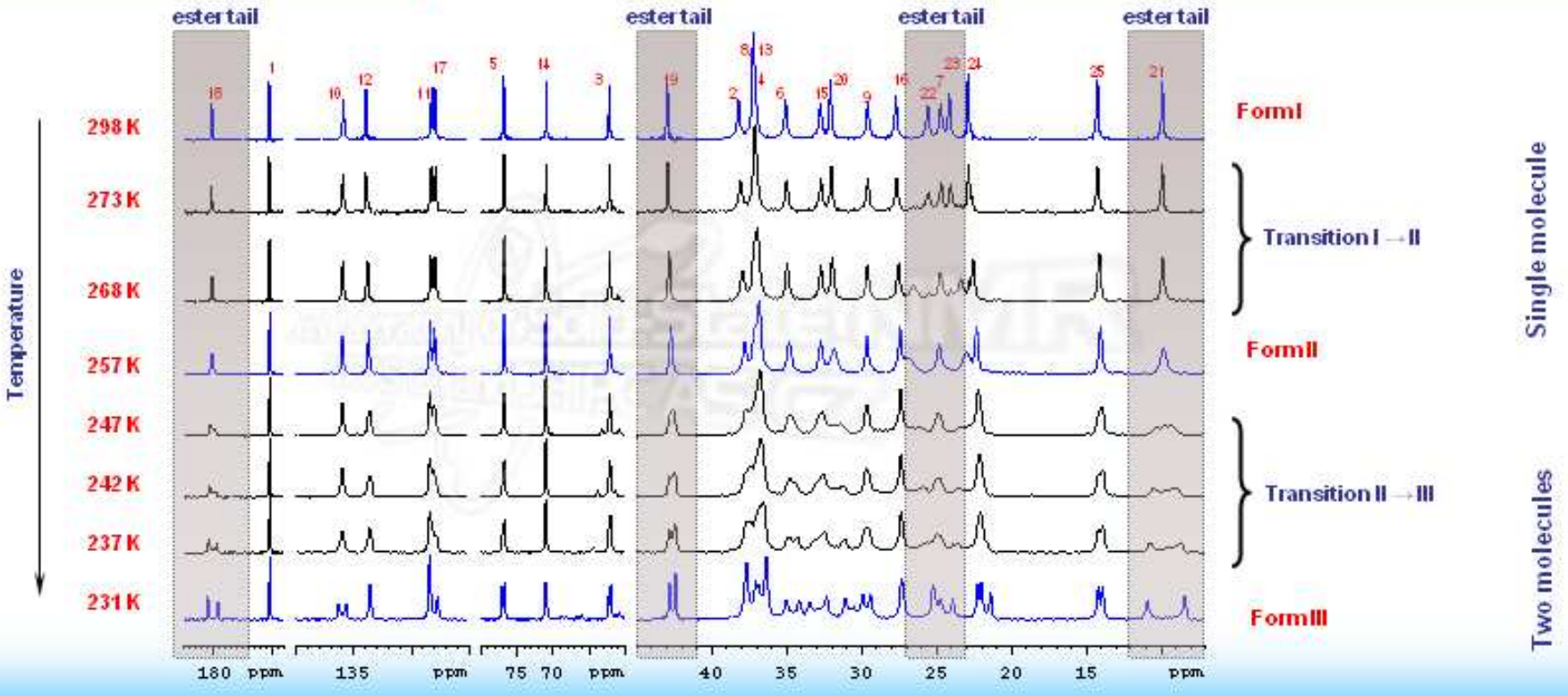
"Every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound"

McCrone, W. 1963



FormI (single molecule)

VT ^{13}C CP/MAS NMR



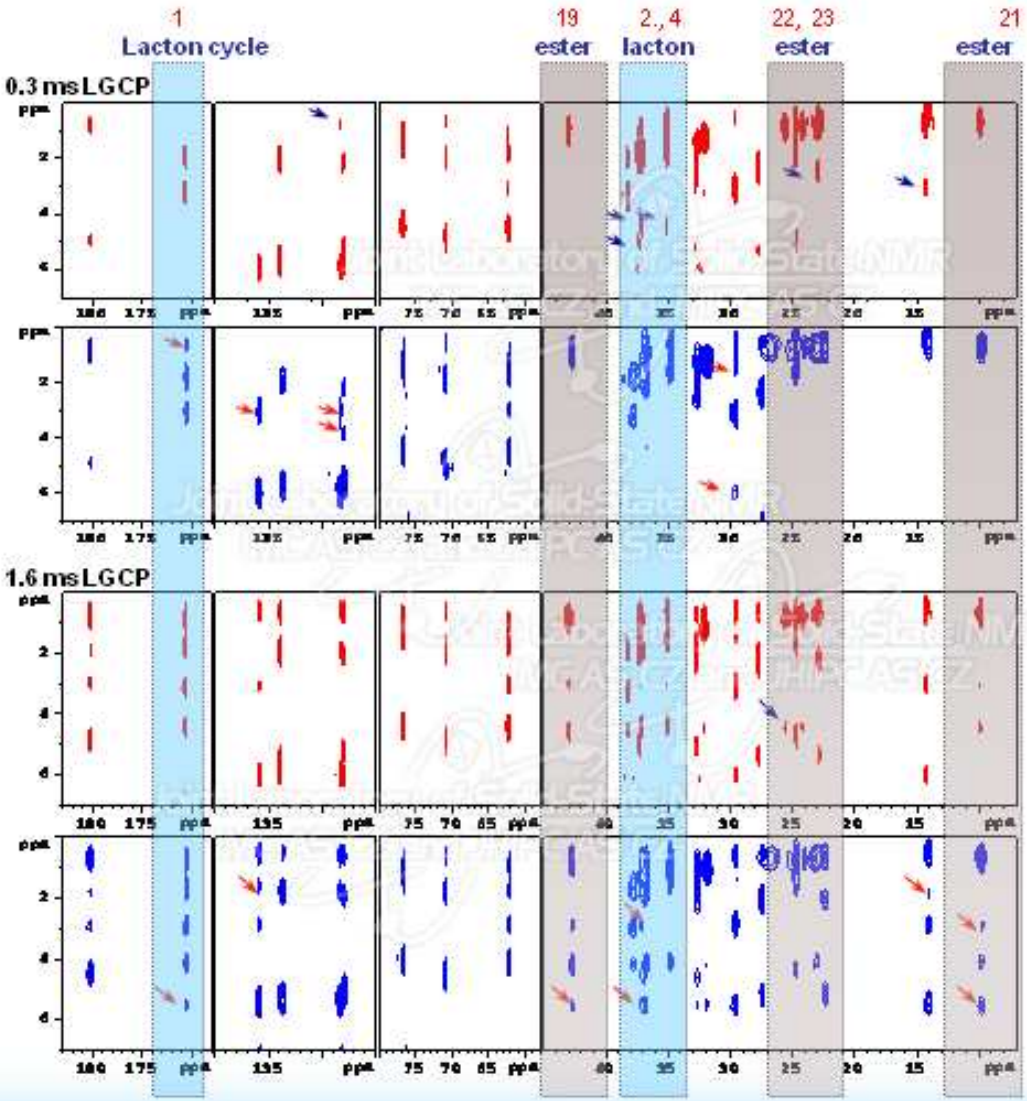
Low-temperature polymorphs of simvastatin

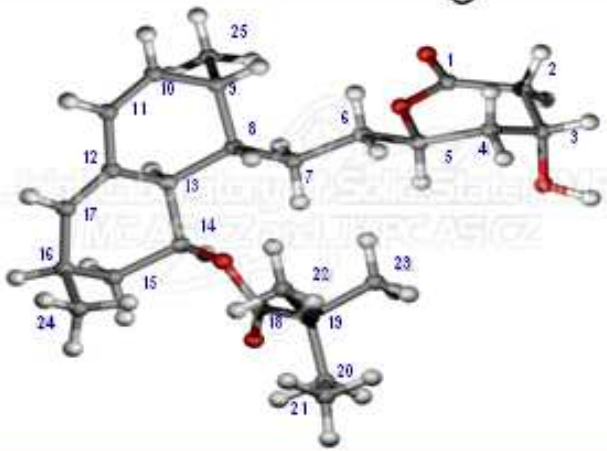
Joint Laboratory of Solid-State NMR
IMC AS CR and JHIPC AS CR

Simvastatin (Zocor®)

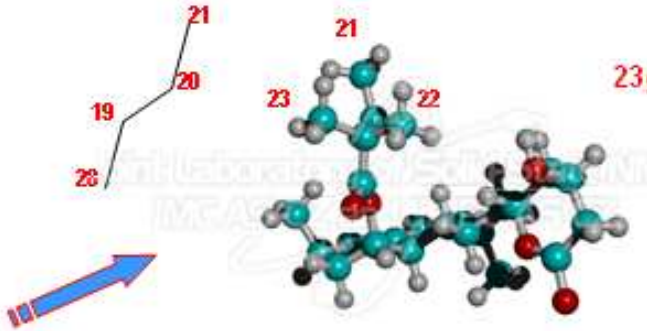
Merck

VT2D ^{13}C-^{1}H FSLG-LGCP HETCOR





Resulting conformation differences of the ester tail



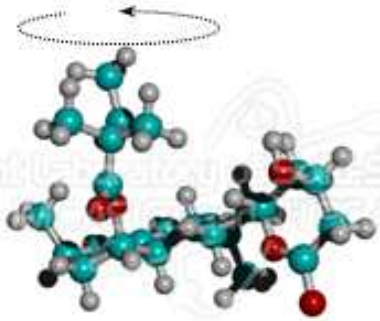
Conformational polymorphism of simvastatin

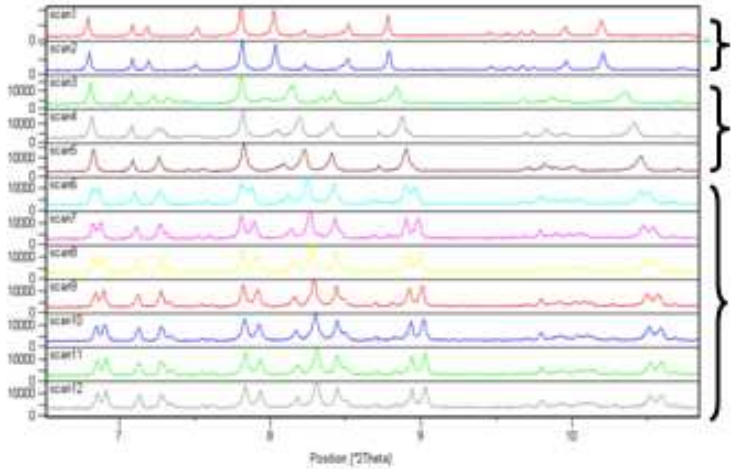
Joint Laboratory of Solid-State NMR
IMC AS CR and JHIPC AS CR

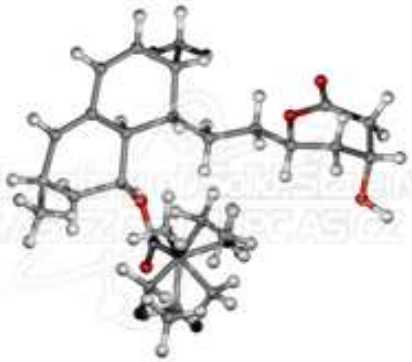
Structure refinement of PXRD data

Form I

23g⁺22g⁻ & 120° jumps

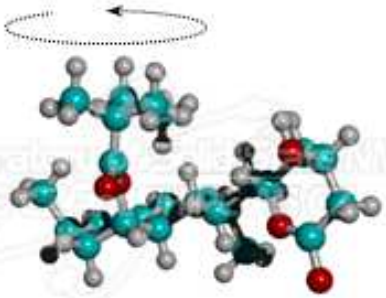






Form II

23t 22g⁺ & 120° jumps

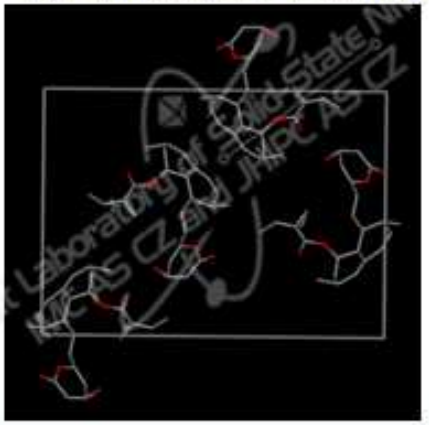


PXRD

Refined structure – Form I

PXRD

Refined structure – Form II



Form I – dynamic disorder of the ester tail in the conformation 23g⁺22g⁻

Form II – dynamic disorder of the ester tail in the conformation 23t 22g⁺

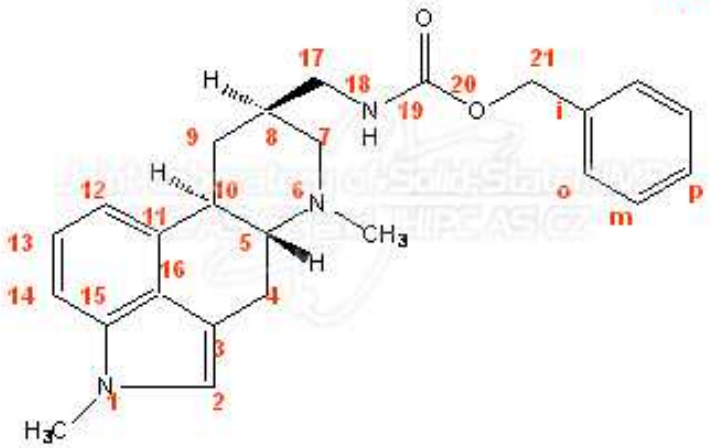
Form III – two static positions of the ester tail in the conformation 23t 22g⁺

Polymorphism of metrgoline

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

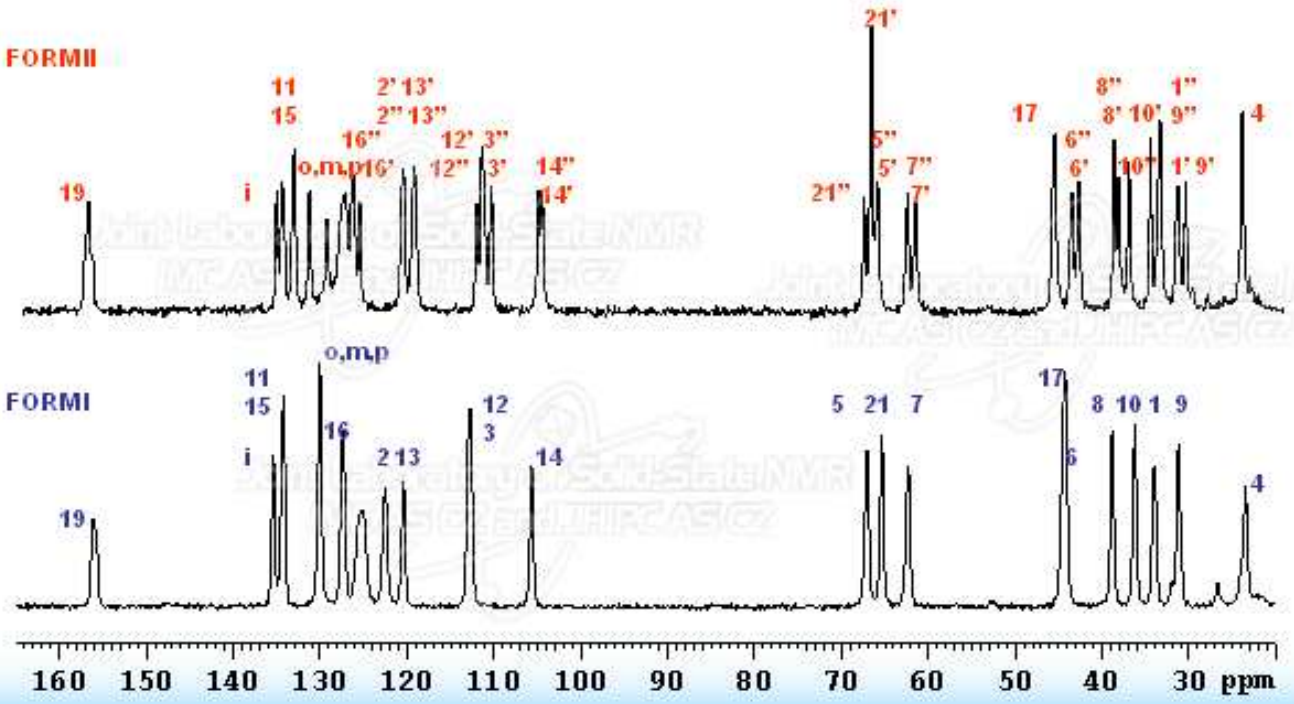
Metergoline (Contralac®)

Virbac AG



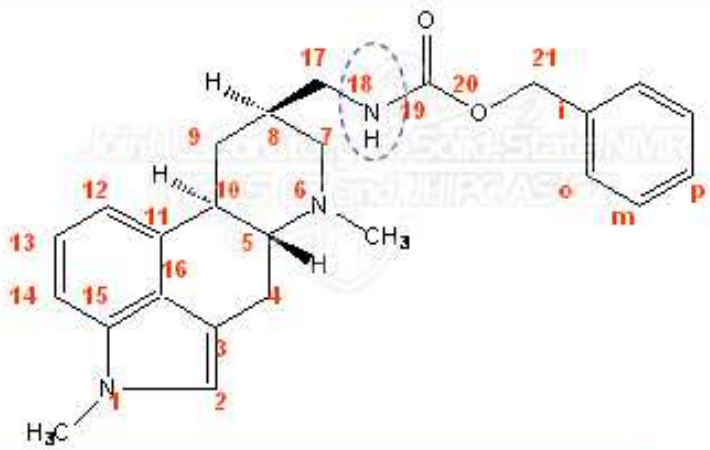
Metergoline, a prolactin (PRL)-lowering drug with an antiserotoninergic activity is usually used for migraine therapy.

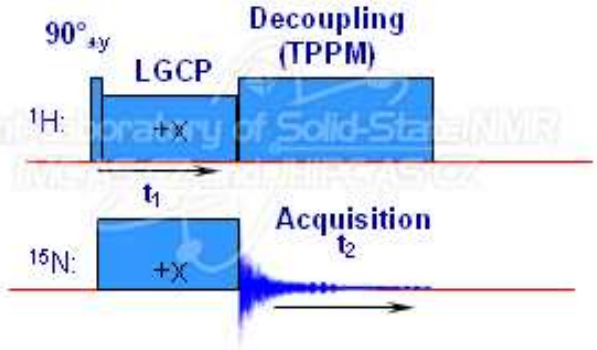
^{13}C CP/MAS NMR



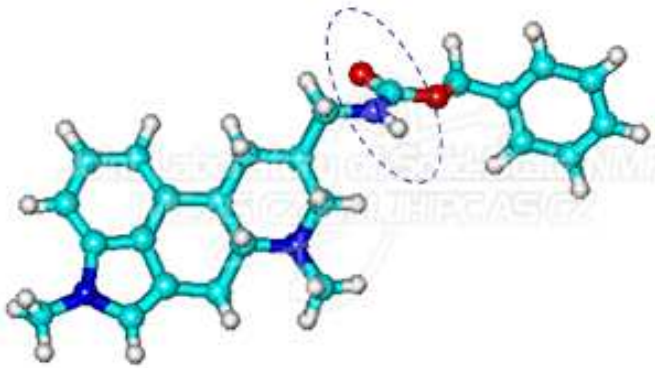
Polymorphism of metrgoline

Hydrogen bonding





N-H group

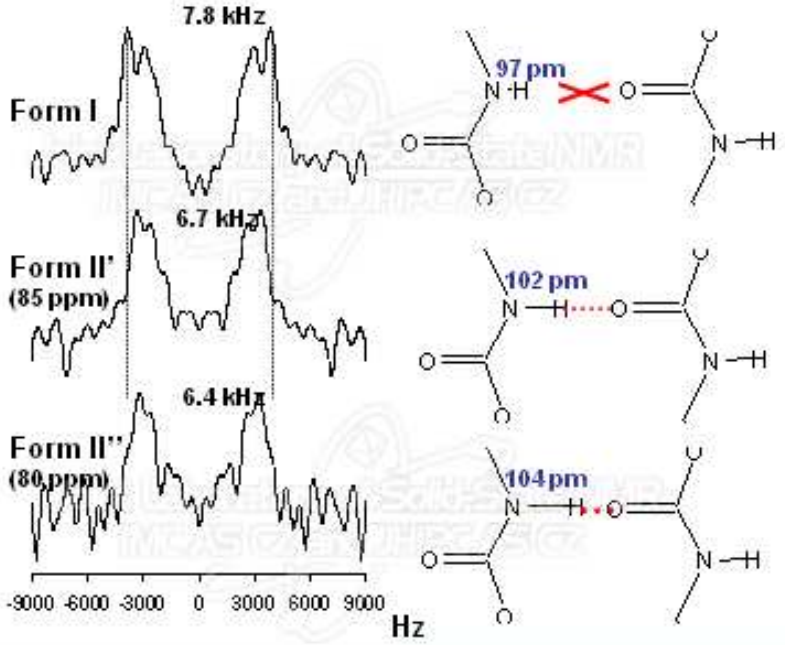


^{1}H-^{15}N dipolar spectra

$$S = \frac{\omega_d}{\sqrt{2}} \sin\theta_m$$

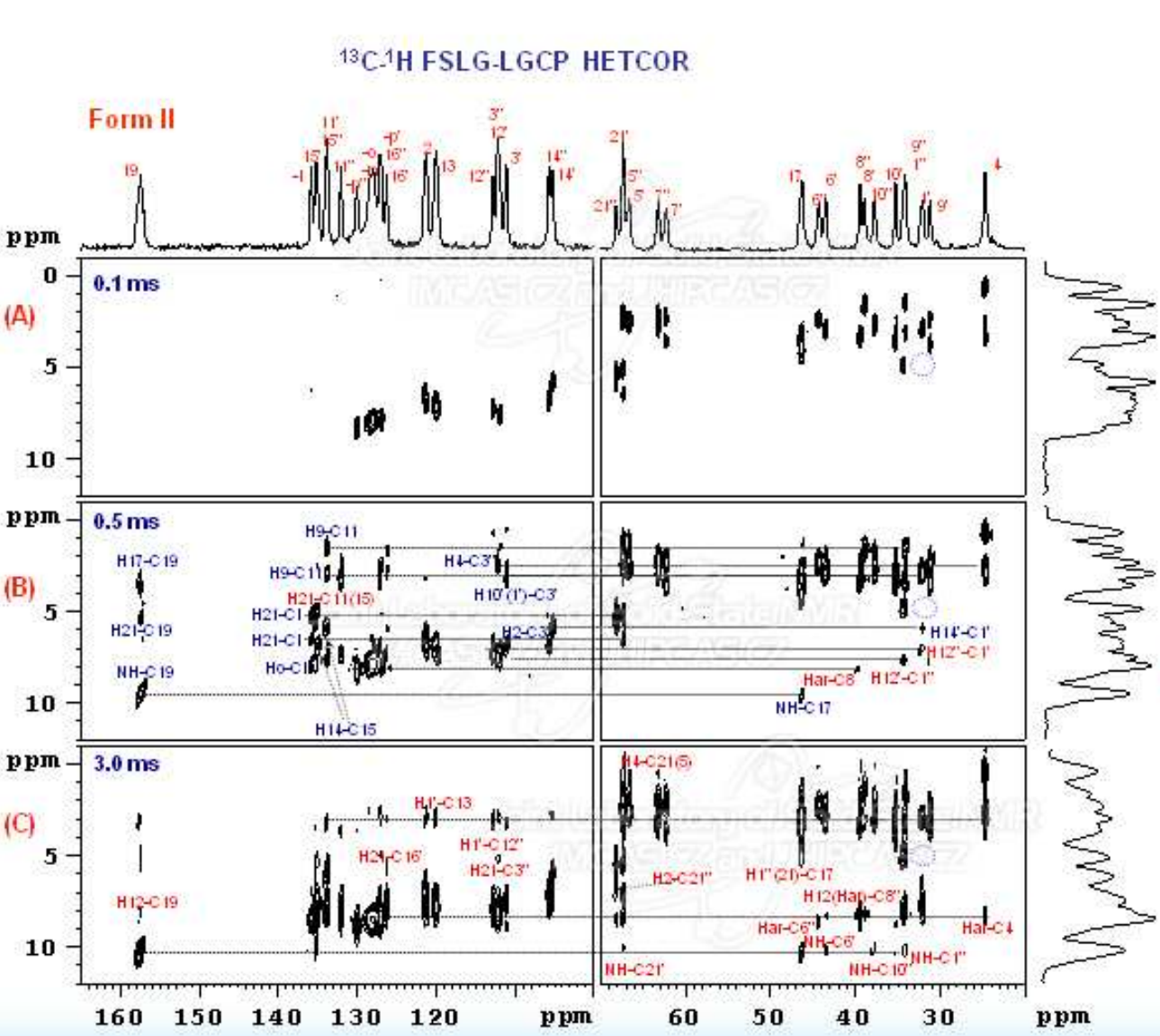
$$\omega_d = \frac{\mu_0}{4\pi} \frac{\gamma_{1H}\gamma_{15N}}{(r_{1,2})^3}$$

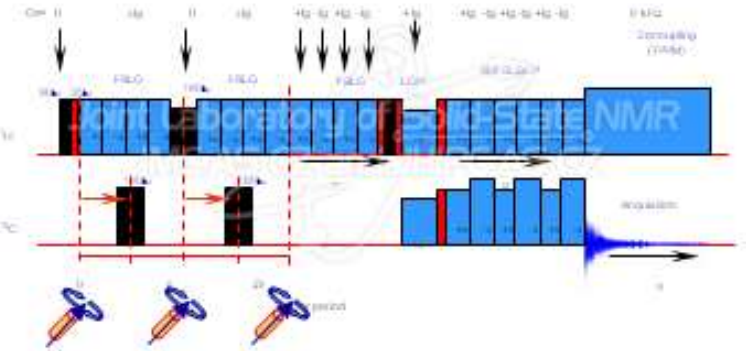
^{1}H-^{15}N distance

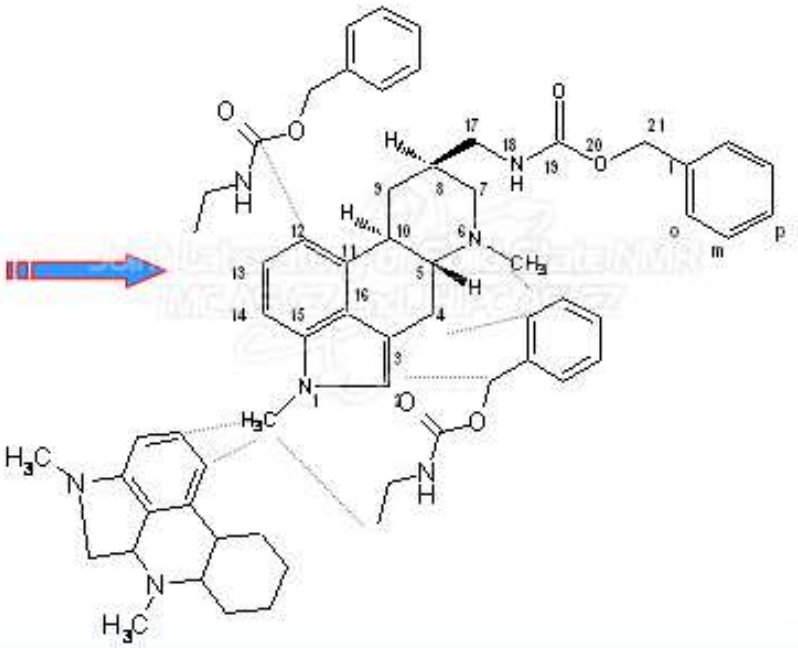


Polymorphism of metrgoline

Structural fragments

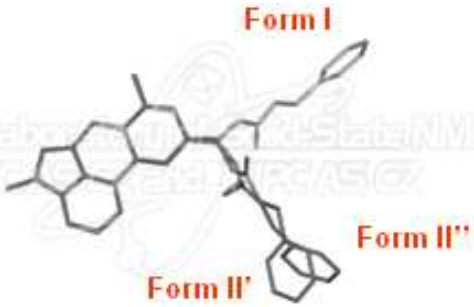






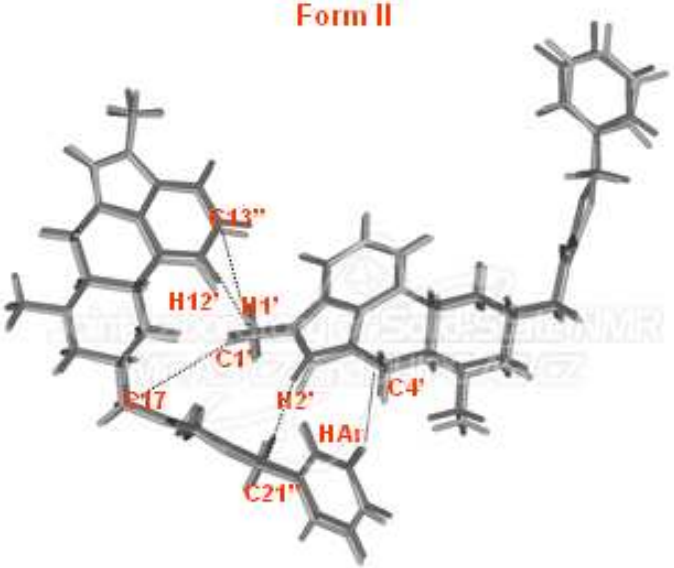
Polymorphism of metrgoline

Structural fragments
Comparison with PXRD results

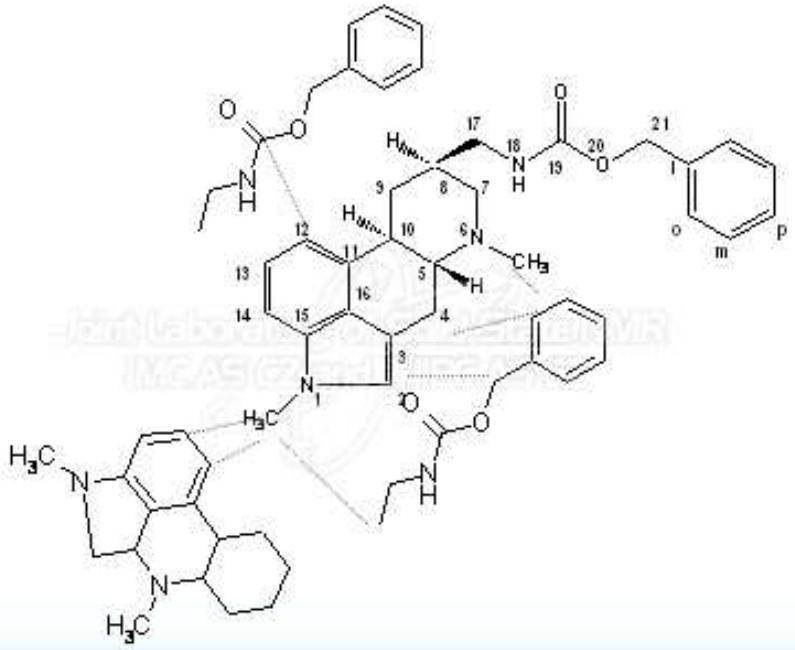


PXRD and single crystal x-ray

Form II



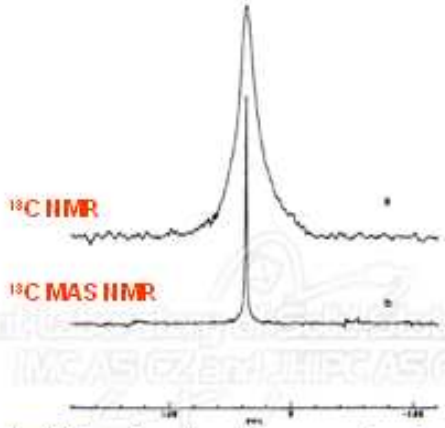
ssNMR



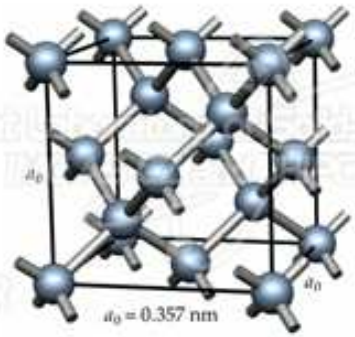
NMR crystallography

Completely immobilized carbon atoms

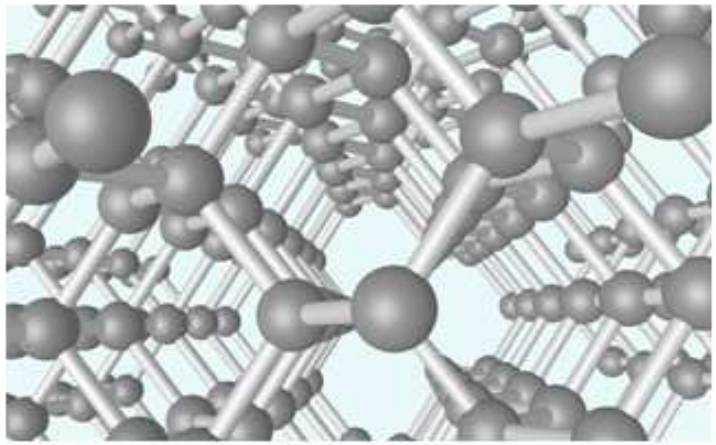
Diamond



T_1 (^{13}C) relaxation time – up to 2 days



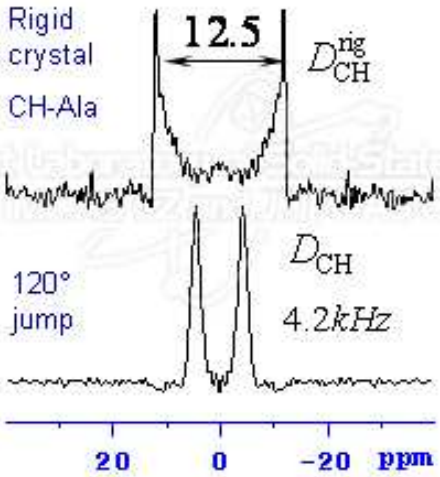
„Diamond is the best friend of woman"
(James Bond, 1971, "Diamonds are forever").



NMR crystallography

Dipolar couplings and segmental dynamics

Dipolar spectrum



Order parameter

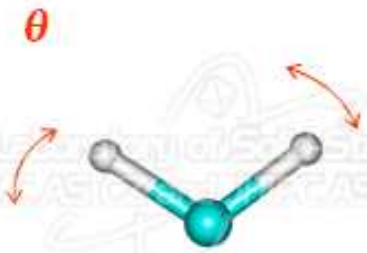
$$S_{CH}^2 = \sum_{i,j=1}^{N} p_i p_j P_2(\cos\theta_{ij})$$ Fast jumps

$$S_{CH} = \frac{D_{CH}}{D_{CH}^{rig}} = \frac{D_{CH}}{12.5(\text{kHz})}$$

$$S_{CH} = 1 - \frac{3}{2}\langle\theta^2\rangle$$ Uniaxial rotational diffusion motion

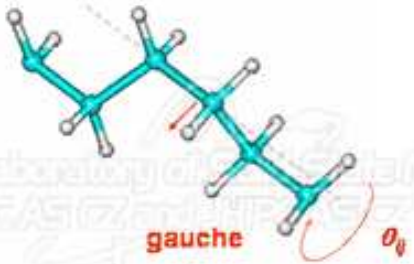
$$S^2 = 1 - 3\sin^2\theta\left\{\cos^2\theta\left(1 - \exp\left[-\sigma_f^2\right]\right) + 0.25\sin^2\theta\left(1 - \exp\left[-4\sigma_f^2\right]\right)\right\}$$ Motion on the cone in parabolic potential

Motional models



Uniaxial rotational diffusion motion

Motion on the cone in parabolic potential



Fast jumps

Polymorphism of metrgoline

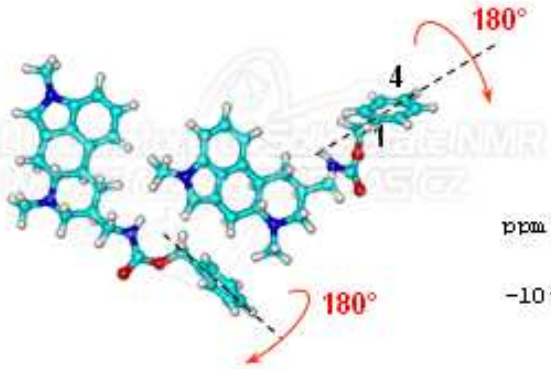
Differences in segmental dynamics

Form II

Order parameter: $S=0.51$

Motional model: $S_{CH}^2 = \sum_{i,j=1}^{N} p_i p_j P_2(\cos\theta_{ij})$
(fast jumps)

Average fluctuation angle: $\theta_{ij} = 126^\circ$



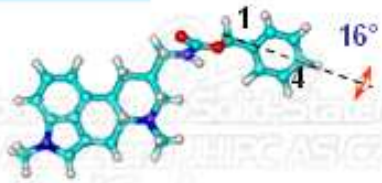
Two-site 180° jumps along (1,4) axis

Form I

Order parameter $S=0.92$

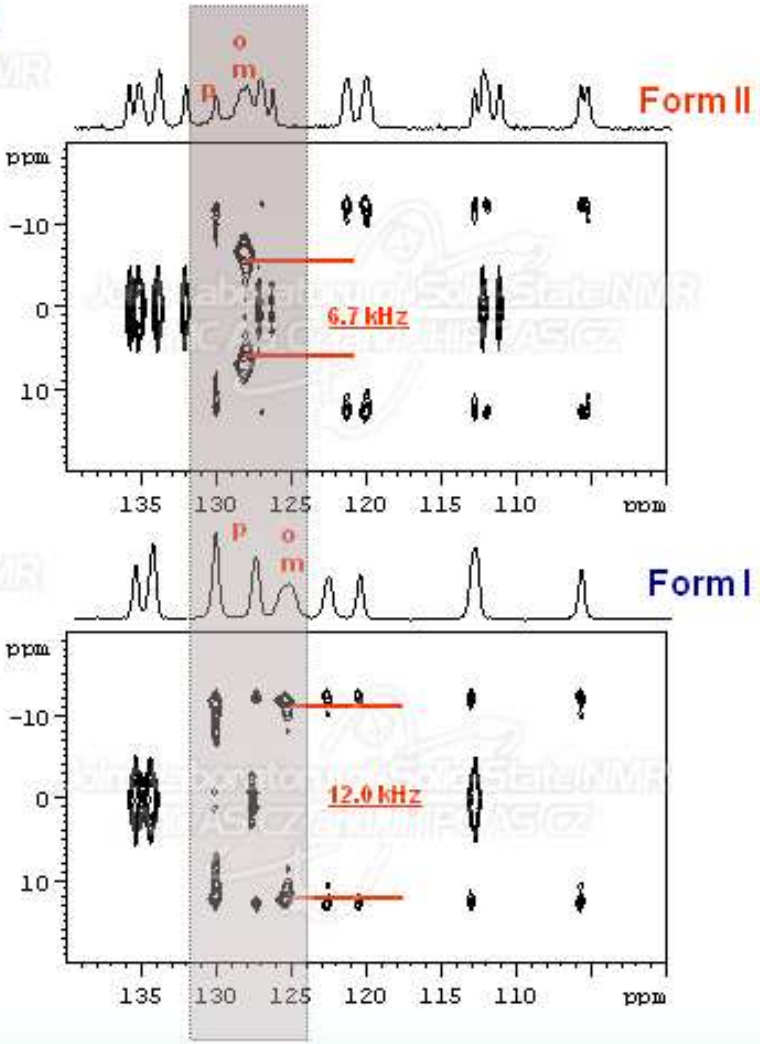
Motional model: $S^2 = 1 - 3\sin^2\theta\{\cos^2\theta(1-\exp[-\sigma_f^2]) + 0.25\sin^2\theta(1-\exp[-4\sigma_f^2])\}$
(motion on the cone in parabolic potential)

Average fluctuation angle: $\sigma = 16^\circ, \theta_0 = 60^\circ$



Small-amplitude 16° oscillation along (1,4) axis

^1H-^{13}C dipolar spectra



Dipolar spectra & ssNMR crystallography

Summary

I) Conformation of single molecule

II) Fragments of molecular arrangement

III) Input data for refinement of PXRD results

IV) Segmental dynamics and motional amplitudes

V) And what about practical results?

Is there any connection between molecular properties determined by ssNMR and macroscopic behavior of API's?

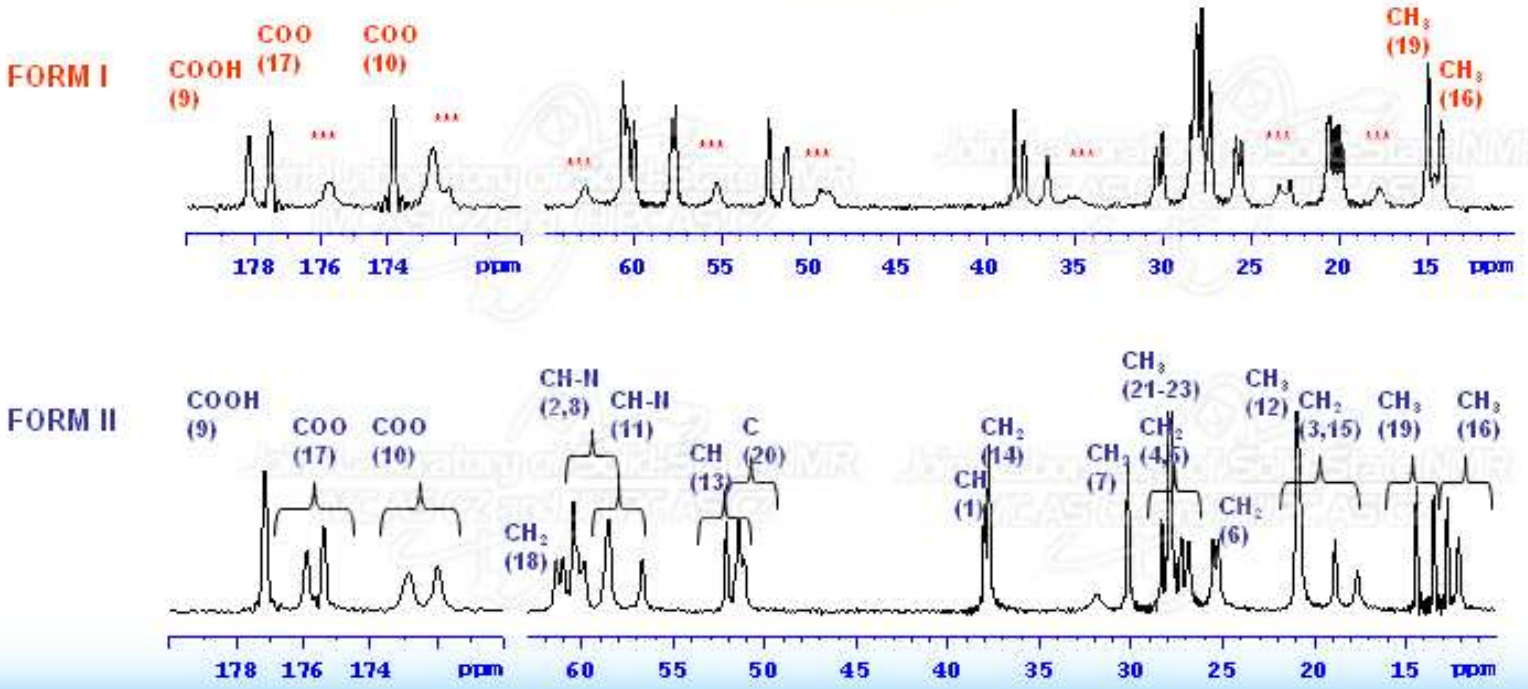
Dipolar spectra & ssNMR crystallography

Dynamic disorder and crystal stability

Form I
thermodynamically most stable form - prepared by slow crystallization from aprotic solvents or by moderate short-term heating of other forms (always broad and narrow signals detected in NMR spectra)

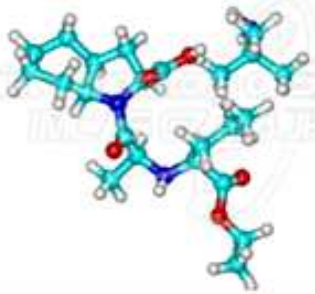
Form II
less stable form containing two symmetry independent molecules in the crystal unit, irreversibly converts to the Form I

^{13}C CP/MAS NMR

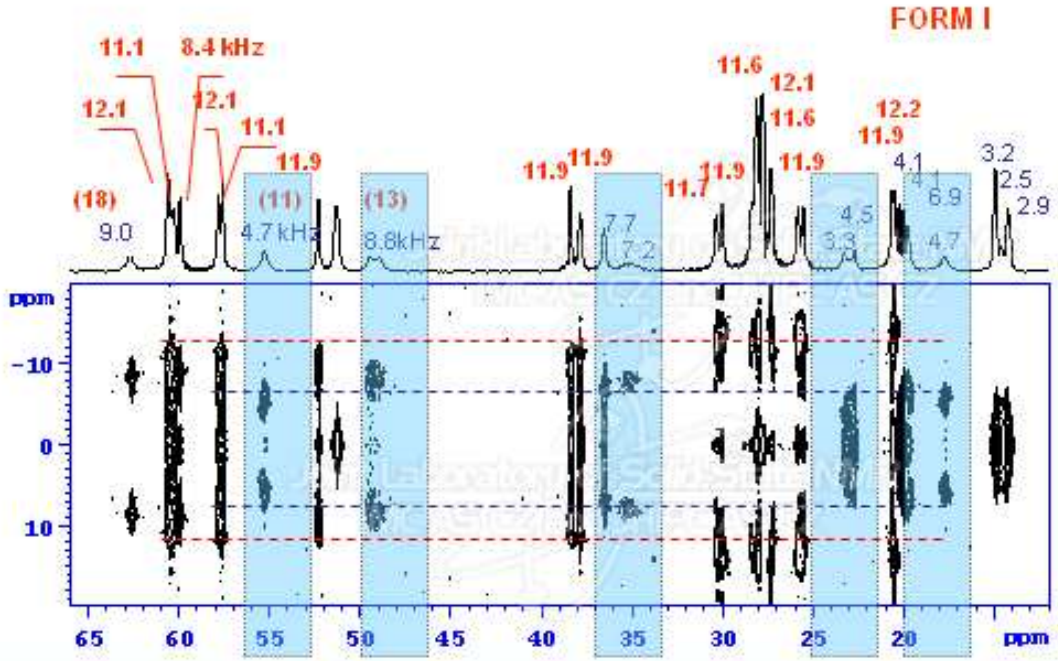


Dipolar spectra & ssNMR crystallography

Dynamic disorder and crystal stability



^{1}H-^{13}C dipolar spectrum



Form I
ca. 30% of molecules have undefined conformation, the observed disorder is dynamic (high amplitude segmental motion is detected)

Order parameter: (determined from dipolar spectra)

S = (0.36) 0.55-0.94

Rotational diffusion motion model: $S_{CH} = 1 - \frac{3}{2}\langle \theta^2 \rangle$

Average fluctuation angle of disordered fractions:

$$\theta = 30 - 40^{\circ}$$

Upper bound of Gibbs energy

$$\Delta G = -kT \sum_{n} \ln\left(\frac{1 - S_{n2}^{2}}{1 - S_{n1}^{2}}\right)$$

transition: **Form II → Form I**
(i.e. increase in conformation entropy at given temperature, stabilization energy)

$$\Delta G = -6.7\,\mathrm{kJ/mol}$$

Acknowledgement

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

Martina Urbanova
Libor Kobera
Jiri Kotek
Jiri Czernek
Antonin Sikora

INSTITUTE OF CHEMICAL TECHNOLOGY PRAGUE

Michal Hušák
Bohumil Kratochvil
Jan Čejka

Grant: 2B08021 MEYS, NPI-II, 2008-2011
Grant: IAA400500602, GA AV CR, 2006-2010