NMR crystallography – structure refinement (simvastatin)

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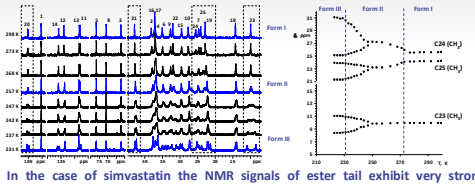
ss-NMR

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

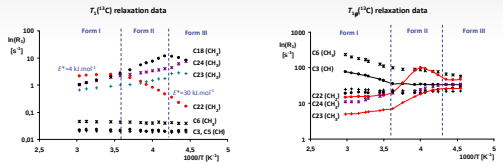
Variable-temperature NMR experiments clearly identify molecular fragments that are most affected by the crystal-phase transition.



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 in well defined conformations.

Motional frequencies – VT T_1 relaxation

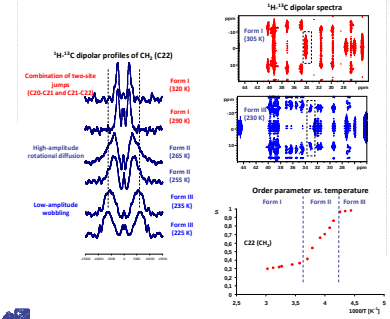
Molecular dynamics substantially affects physical properties of many organic solids. T_1 and $T_{1\rho}$ NMR relaxation measurements provide valuable information about motional frequencies of molecular segments in wide range .



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.



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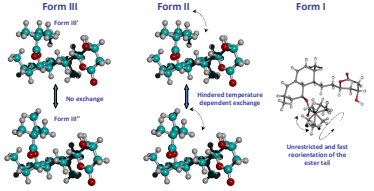
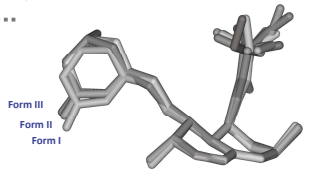
NMR crystallography

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.

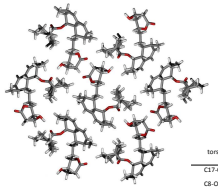
Structural and motional motifs



Static XRPD structure



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

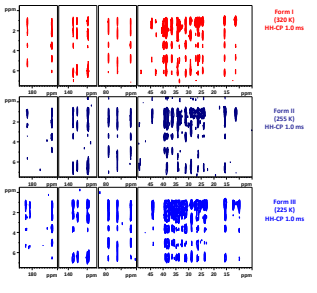


	form I	form II	form III
formula		$C_{25}H_{38}O_5$	
M.w.		418.57	
absorption coefficient (mm^{-1})	0.08	0.08	0.08
crystal system	orthorhombic	orthorhombic	monoclinic
space group , Z	$P2_12_12_1$, 4	$P2_12_12_1$, 4	$P2_1$, 4
a, Å	6.1251(1)	6.0914(4)	6.0237(3)
b, Å	17.3137(3)	16.727(1)	16.2164(7)
c, Å	22.4636(4)	23.147(1)	23.465(1)
β, (°)	90	90	89.067(2)

torsion angle	form I (higher occupancy conformation)	form I (lower occupancy conformation)	form II	form III molecule 1	form III molecule 2
C17-C8-O4-C20	-158.7	-158.7	-159.0	-163.8	-163.0
C8-O4-C20-C21	172.0	172.0	172.6	165.9	173.0
O4-C20-C21-C22	-26.3	155.2	137.5	13.58	48.3
C20-C21-C22-C23	174.8	138.4	172.9	-141.2	-77.6
C17-C16-C7-C6	-169.8	-169.8	-161.8	-159.7	-153.4
C16-C7-C6-C5	174.8	174.8	-163.1	-168.4	-161.2
C7-C6-C5-O1	72.5	72.5	73.4	71.7	68.2

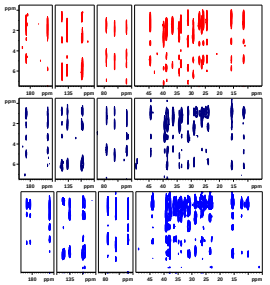
^{1}H-^{13}C (^{1}H-^{1}H) contacts FSLG HHCP HETCOR

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

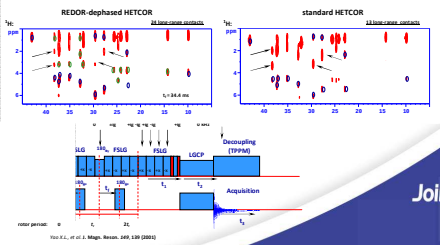
A bit different correlation pattern is provided by HETCOR experiments in which ^{1}H-^{1}H spin exchange is suppressed by Lee-Goldburg cross-polarization.



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

Suppression of one-bond correlation signals increases number of structurally more important long-range contacts.

Form I: 25 → 40; Form II: 27 → 43; Form III: 31 → 49.



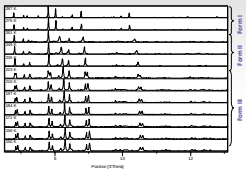
XRPD

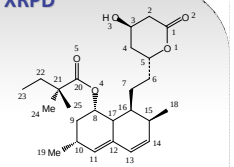
X-ray diffraction on single crystals provides the "golden standard" of molecular structure analysis. In absence of suitable single crystals the diffraction on powdered samples (XRPD) is applied. Structure determination, however; is not straightforward even from synchrotron data. Distance restraints and 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

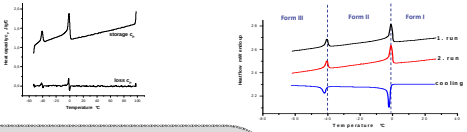




There are only slight differences between all three phases, but the differences still significantly affect the powder diffraction pattern. From the terminology point of view it would be interesting to discuss, if such slight conformation changes accompanying the phase transformation I to II are enough 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