NMR crystallography for structure refinement of low-temperature polymorphs

Jiri Brus, Martina Urbanova, Olivia Policianova

[†] *Department of Structure Analysis, Institute of Macromolecular Chemistry, Heyrovsky sq. 2, 162 06 Prague 6, Czech Republic*

Abstract

The concept of NMR crystallography – a combination of the advanced techniques of solid-state NMR with x-ray powder diffraction and molecular computation – is applied to comprehensively describe structure and molecular dynamics of the recently discovered low-temperature crystal modifications of simvastatin.
Although the conformational flexibility of the molecule of simvastatin just invites to easy crystallization in various modifications the reported new crystal forms belong to the family of “extreme” or “low-temperature” polymorphs. It was found out that simavastatin exhibits enantiotropic behavior with transition temperatures occurring at -1℃ and -41℃. Although these “extreme” polymorphs have litt le significance for pharmaceutical industry the detail analysis of their behavior in the wide temperature range made it possible to detect site-specific structural motifs and motional processes that allowed thermally induced solid-solid transitions. On the other hand it is demonstrated that very these motifs and process do not allow extensive polymorphism.
As the discovered low-temperature crystal modifications do not provide suitable single crystals the presented contribution also demonstrates a successful application of NMR-assisted x-ray powder crystallography for the determination of complete crystal structures and for the comprehensive analysis of motional behavior. It is clearly demonstrated that the analysis of ^{13}C NMR chemical shifts, high-level quantum chemical calculations together with sufficiently large set of long-range ^{1}H-^{13}C dipolar contacts provide geometrical restraints making x-ray powder crystal structure refinement much easier and more reliable.
In the presented study the particular attention was paid to the enhancement of the number of long-range ^{1}H-^{13}C correlation signals, and the potential of REDOR-dephasing ^{1}H-^{13}C FSLGCP HETCOR technique is demonstrated. The unexpectedly extensive segmental dynamics was probed in both high- and low-frequency regimes by various relaxation and exchange experiments while motional amplitudes were monitored by PISEMA-type recoupling techniques in the whole temperature range. Furthermore, the obtained structural data were combined and correlated with thermodynamic behavior and the crystal phase transitions and finally the obtained motional models were used to interpret multiple correlations observed in ^{1}H-^{13}C HETCOR spectra and to reconstruct basic structural motifs. These motifs were subsequently used to assist in the crystal-structure refinement of x-ray powder diffraction data. The determined and refined crystal structures are compared.

Acknowledgements: The authors wish to thank the Grant Agency of the Academy of Sciences of the Czech Republic and the Ministry of Education, Youth and Sports for financial support (projects IAA400500602 and 2B08021, respectively).