Summary

Polymorphism is the ability of a compound to crystallise in more than one crystal structure. When a polymorphic form of a compound is not the stable form at a certain temperature and pressure, solid-state phase transitions can occur. The mechanism of solid-state phase transitions has been under much debate, but the nucleation-and-growth theory of Mnyukh is mostly accepted by the community. However, in case the two polymorphic forms involved have similar crystal structures, there is an ongoing debate if the phase transition mechanism could involve cooperative motion of molecules. The term 'cooperative motion' is used in this work for the simultaneous movement of multiple neighbouring molecules, on a limited length scale of tens to a few hundreds of molecules. This is different from cooperative motion in second-order phase transitions with an infinite correlation length. This work describes the study of the solid-state phase transitions of linear amino acids as a model system for molecular crystals that can involve cooperative motion. These amino acids have similar crystal structures and reversible single-crystal-to-single-crystal phase transitions. Therefore, this thesis contributes to the understanding of the mechanism of these solid-state phase transitions on a molecular scale.

This thesis opens with a general introduction in Chapter 1, which introduces the topic and scope of the thesis. Chapter 2 gives an overview of the theory on polymorphism and phase transitions, with an emphasis on nucleation-and-growth theory, cooperative motion in thermosalient crystals, and amino acid crystals.

The phase transitions of the amino acid DL-norleucine (DL-Nle) are studied in detail in Chapters 3 and 4. Chapter 3 describes the low temperature $\beta \leftrightarrow \alpha$ phase transition of DL-Nle in a combined computational and experimental study. It shows that the β and α forms of DL-Nle are nearly identical from a structural perspective and the same holds for the energies as a function of temperature. Computational modelling in the form of molecular dynamics (MD) and nudged elastic band (NEB) calculations suggest the phase transition is governed by cooperative motion of bilayers. In Chapter 4 both the low temperature $\beta \leftrightarrow \alpha$ and high temperature $\alpha \leftrightarrow \gamma$ phase transitions of DL-Nle are studied in detail using DSC, thermal stage polarisation microscopy and solid-state NMR. Remarkably, single crystals of DL-Nle show much faster

kinetics than powders for the $\beta \leftrightarrow \alpha$ phase transition, which is attributed to the inhibitory effect of defects on cooperative motion. This chapter also shows that traditional methods of polymorph screening might overlook some solid-state phase transitions similar to the $\beta \leftrightarrow \alpha$ transition in DL-Nle, while methods such as single crystal DSC and solid-state NMR can be used to reveal them.

In Chapter 5 the solid-state phase transition of DL-methionine (DL-Met) is studied in detail. This phase transition is kinetically hindered, and is shown to be significantly faster during heating than during cooling. A large temperature range with coexistence of the two forms in one crystal is shown by solid-state NMR. Again, the phase transition is faster in single crystals than in powders, indicating the important role of defects on the kinetics.

The focus of Chapter 6 is on the five new enantiotropically related polymorphic forms of DL-2-aminoheptanoic acid (DL-Hep) and their solid-state phase transitions. Two low temperature forms were refined in a high Z' crystal structure, which has not been observed before for linear aliphatic amino acids. All five structures consist of the typical 2D hydrogen-bonded bilayers, and the phase transitions involve shifts of bilayers and/or conformational changes in the aliphatic chain. Compared to two similar phase transitions of DL-Nle, the enthalpies of transition and NMR chemical shift differences are notably smaller in DL-Hep. This is explained to be a result of both the nature of the conformational changes, and the increased chain length.

In Chapter 7 two new crystal structures and the solid-state phase transition between them are described for the quasiracemate D-2-aminobutyric acid:L-norvaline (D-Abu:L-Nva). Quasiracemates of linear amino acids, consisting of two similar D and L amino acids, generally show crystal structures similar to the racemates. This is also the case for D-Abu:L-Nva. The room temperature form II shows two conformations for the L-Nva side chain in a disordered 50/50 occupancy distribution, which can be understood from steric hindrance.

Chapter 8 describes the influence of the difference in chain length between two amino acid enantiomers comprising a quasiracemate, on the crystal structures and solid-state phase transitions. New quasiracemates have been discovered consisting of aminoheptanoic acid or aminooctanoic acid with a long linear aliphatic chain, combined with shorter linear chain amino acids. The quasiracemates with a significant chain length difference between the two enantiomers show different stacking patterns of the aliphatic chains and hydrogen bonding patterns, to reduce steric hindrance.

Chapter 9 describes the phase transitions of the pharmaceutical compound pyrazinamide (PZA). In this thesis, it is shown that the phase transition from γ-PZA to the low temperature forms involves a vapour-mediated recrystallisation, while the reverse phase transition upon heating is a nucleation-and-growth solid-solid phase transition. Moreover, when PZA is co-spray dried with 1,3-dimethylurea (DMU), it has been reported to remain in its γ form for

several years. The lifetime-extending effect of DMU on spray-dried PZA has been investigated in more detail and compared with high-energy ball milling of sublimation-grown γ-PZA crystals in this thesis. DMU acts as an additive that most likely stabilises the surface of γ-PZA, which would reduce the vapour pressure of PZA, thereby reducing the transition rate. Alternatively, DMU could prevent nucleation of low temperature forms.

This thesis concludes with a final Chapter 10 that reviews most of the findings in literature and this thesis on phase transitions in linear amino acids, including new phase transition characteristics of (quasi)racemates with longer aliphatic chains. Cooperative motion on a limited length scale is shown to be compatible with the nucleation-and-growth theory for the mechanism of solid-state phase transitions of molecular crystals.