



Effect of type and extent of crystalline order on chemical and physical stability of carbamazepine

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Abstract

Three crystalline phases of carbamazepine (C), namely (i) the needle-shaped form **I** (tempered) with high crystalline order, (ii) beam-shaped form **I** (anhydrate) with lower crystalline order, which was prepared by dehydration of the dihydrate, and (iii) the prismatic form **III**, which is stable at room temperature, were prepared and their physical properties were determined. Then they were separately mixed with 40% (w/w) colloidal silica and stored open under climatic stress at 4 temperatures (56–72°C) and 3 relative humidities (41–71%). The physical and chemical stability of C was followed for 200 days. Form **I** (anhydrate) transformed under all conditions to form **III**, with the highest rate at 51°C, while the other phases were physically stable. C degraded chemically by hydrolysis to iminostilbene (IS); about 10 mol% were formed at the highest stress after 200 days. Small amounts of secondary products were detected. An initial constant degradation rate up to 1 mol% IS was followed by a slower, again linear degradation. The initial rates of formation of IS per unit surface area of the crystals ($^{\circ}\text{k}$, mol%/day) were highest for form **I** (anhydrate) and lowest to form **I** (tempered). The calculated Arrhenius activation energies up to 67°C

were of the order form **III** > form **I** (anhydrate) > form **I** (tempered) with 135, 125 and 104 kJ/mol, respectively. The energies of activation for chemical degradation correlate well with the content in free enthalpy of the respective crystalline phases and their correspondent physical stability.

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