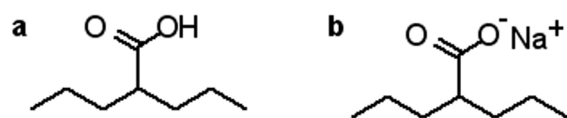


Fourier Transform Infrared Spectroscopic Analysis of the Solvates and Polymorphs of Sodium Valproate, Active Component of the Anticonvulsant Drug Epilim[®]

G. Petruševski¹, P. Naumov^{1,2}, G. Jovanovski^{1,3}

¹*Institute of Chemistry, Faculty of Science, SS. Cyril and Methodius University, POB 162, MK-1001 Skopje, Macedonia,* ²*Graduate School of Engineering, Osaka University, 2-1 Yamada-oka, Osaka, Suita 565-0871, Japan,* ³*Macedonian Academy of Sciences and Arts, POB 428, MK-1001, Skopje, Macedonia*

2-Propylvaleric (valproic) acid and its sodium salts (Scheme 1) have been extensively clinically used as anticonvulsants and mood-stabilizing drugs to treat cases of epilepsy and bipolar disorders, diseases which affect approximately 1% of the human population. Although sodium valproate has been used as medicine for more than fifty years, until recently [1,2], no detailed studies of the polymorphism and crystal structure of this compound were performed. Here, we report the first systematic study of the solid state solvates and polymorphs of sodium valproate, as studied with Fourier transform infrared (FTIR) spectroscopy. Using wet and dry methods, as many as seven solid forms and one thermal intermediate (denoted forms A, B, C, D, E, F, G and H) were prepared. Three compounds (forms A, B and D) are extremely hygroscopic polycrystalline hydrates, three compounds (forms C, E and F) are stoichiometric solvates of sodium valproate with valproic acid, and one compound is an anhydrous salt (form H). Forms A, B and C are unstable upon evacuation and pressing with KBr, and under such treatment they are converted into form D. On the contrary, forms E and F are stable under ambient conditions.



Scheme 1: Formulas of valproic acid (a) and sodium valproate (b).

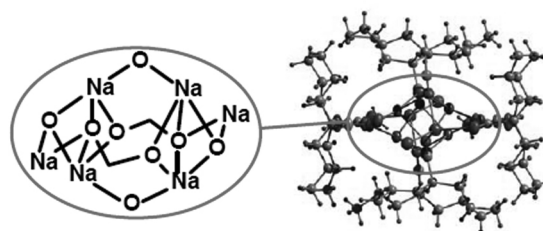


Figure 1: Crystal structure of form C, trisodium hydrogentetravalproate monohydrate.

It is concluded that the spectra recorded from milled samples are sufficiently descriptive to distinct among different polymorphic forms of sodium valproate. Most useful band in the infrared spectra is the antisymmetric carboxylate stretching vibration (1552–1570 cm^{-1}). The frequency split between the antisymmetric and symmetric carbonyl stretches (1413–1441 cm^{-1}), combined with the molecular geometry as determined for the crystal of the form C [1] (Fig. 1), was used to correlate the structural preferences of the carboxylate ion in the other forms of unknown structure. Theoretical calculations were also performed in order to assign the characteristic IR bands, to correlate the spectral appearance with the structural data, and to predict structural features of the sodium valproate forms of unknown structure.

[1] G. Petruševski, P. Naumov, G. Jovanovski, S.W. Ng, *Inorg. Chem. Commun.* 11 (2008) 81–84.

[2] G. Petruševski, P. Naumov, G. Jovanovski, G. Bogoeva-Gaceva, S.W. Ng, submitted for publication.