MS28-2-4 GABA and gabapentin - commonalities and distinctions in (co-)crystallization behaviour from molecular conformation to crystal lattice
#MS28-2-4

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Abstract
γ-Amino butanoic acid (GABA) is a simple non-essential amino acid from which manifold active pharmaceutical ingredients (APIs) are derived. The antiepileptic drug Gabapentin (2-(1-(aminomethyl)-cyclohexyl) acetic acid) is one of its most commercially successful analogues. In this work commonalities and distinctions in their crystallization behaviour are elucidated on. In the past, various publications have established indicators of stability for either single molecular conformations or crystal entities of either GABA[1-3] or Gabapentin[4, 5]. Identification of common structure motifs in congruence with an analysis of lattice energies and molecular conformations are performed on single- and multicomponent crystalline entities. First, two polymorphs of GABA and Gabapentin as well as the Gabapentin hydrate are analyzed in the described manner. In the second step, multicomponent forms of both compounds with either fumaric or succinic acid are used for comparison. It is attempted to answer the questions: Can a favourable molecular conformation be an indicator for crystal phase stability in single and multicomponent crystalline species? Are structural properties of crystalline solid GABA species necessarily comparable to those of a similar derivative? What indicators for a reliably stable GABA related crystalline phase might there be? Lattice energies are calculated via Quantum Espresso PWSCF v. 6.6[6] and analysis of molecular and crystal structure properties is conducted via Mercury 2020.2.0[7] and PLATON[8].
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References
[1] Song, I. K.; Kang, Y. K. Conformational preferences of γ-aminobutyric acid in the gas phase and in water. J. Mol. Struct. 2012, 1024, 163–169. DOI: 10.1016/j.molstruc.2012.04.080.
[2] Wang, L.; Sun, G.; Zhang, K.; Yao, M.; Jin, Y.; Zhang, P.; Wu, S.; Gong, J. Green Mechanochemical Strategy for the Discovery and Selective Preparation of Polymorphs of Active Pharmaceutical Ingredient γ-Aminobutyric Acid (GABA). ACS Sustain. Chem. Eng. 2020, 8 (45), 16781–16790. DOI: 10.1021/acssuschemeng.0c04707.
[3] Lamkowski, L.; Komisarek, D.; Merz, K. GABA-Controlled Synthesis of the Metastable Polymorphic Form and Crystallization Behavior with a Chiral Malic Acid. Cryst. Growth Des. 2022, 22 (1), 356–362. DOI: 10.1021/acs.cgd.1c00991.
[4] Liu, Y.; Wang, Y.; Huang, X.; Li, X.; Zong, S.; Wang, N.; Hao, H. Conformational Selectivity and Evolution Affected by the Desolvation Process. Cryst. Growth Des. 2022, 22 (2), 1283–1291. DOI: 10.1021/acs.cgd.1c01253.
[5] Delaney, S. P.; Smith, T. M.; Korter, T. M. Conformation versus cohesion in the relative stabilities of gabapentin polymorphs. RSC Adv. 2014, 4 (2), 855–864. DOI: 10.1039/C3RA43887B.
[6] Giannozzi, P.; Baseggio, O.; Bonfà, P.; Brunato, D.; Car, R.; Carnimeo, I.; Cavazzoni, C.; Gironcoli, S. de; Delugas, P.; Ferrari Ruffino, F.; Ferretti, A.; Marzari, N.; Timrov, I.; Urru, A.; Baroni, S. Quantum ESPRESSO toward the exascale. Chem. Phys. 2020, 152 (15), 154105. DOI: 10.1063/5.0005082.
[7] Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T. A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M.; Wood, P. A. Mercury 4.0: from visualization to analysis, design and prediction. J. Appl. Crystallogr. 2020, 53 (Pt 1), 226–235. DOI: 10.1107/S1600576719014092. Published Online: Feb. 1, 2020.
[8] Spek, A. L. Single-crystal structure validation with the program PLATON. J. Appl. Crystallogr. 2003, 36 (1), 7–13. DOI: 10.1107/S0021889802022112.