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Synthon competition in new pharmaceutical forms: how crystal structure affects properties

M. Teresa Duarte,[a] Vânia André,[a] Fabrizia Grepioni,[b] Nair Rodriguez-Hornedo,[c] Chinmay Maheshwari,[c] [a]*Centro de Química Estrutural, DEQB, Instituto Superior Técnico, Lisbon, Portugal;* [b]*Dipartimento di Chimica ''G. Ciamician'', Universita di Bologna, Via Selmi 2, 40126 Bologna, (Italy);* [c]*College of Pharmacy, Dept. of Pharmaceutical Sciences, University of Michigan , Ann Arbor, MI 48109, (USA).* E-mail: teresa.duarte@ist.utl.pt

Crystal design and engineering has received much attention in recent years as its implications extend to material science, solid state reactions and synthesis, and drug development.

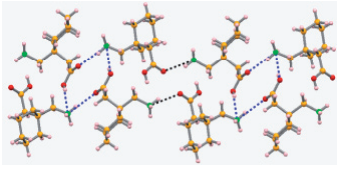
One of the most important issues in this field is the rational design and arrangement of molecular packing, which affects and controls the macroscopic properties of materials. A comprehensive understanding of supramolecular systems is primarily dependent on the knowledge of intermolecular interactions controlling the molecular aggregation, with major emphasis on hydrogen and halogen bonding as well as aromatic stacking.

Synthon formation and breaking is a main key and the driving force in structure-properties relationships.

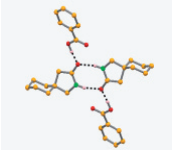
More significant than knowing the structure of new API forms is to correlate that information with the properties of the novel compounds. Stability and solubility are major factor known to strongly affect API's performance and therefore their correlation with structural and thermal data is of upmost importance.

As an example several cocrystals and molecular salts of gabapentin-lactam (GBPL), a prodrug with proven neuroleptic effects, were unveiled and fully characterized; the pH-dependent solubility of these novel forms were studied and a correlation between solubility data, structural information and thermal stability has been purposed.

Studies with gabapentin (GBP), a neuroleptic drug, yielded several multicomponent crystal forms whose thermal and pH stability have also been determined With the antibiotic 4-aminosalicylic acid (4ASA) eleven new crystal forms were disclosed, including polymorphs, solvates, cocrystals, molecular salts and salts. A novel hydrated form of the antihypertensive perindopril erbumine was found, the first molecular structures of this API were determined, and the relative stability compared to the commercial forms were studied



GBP-therephtalic acid



GBPL-benzoic acid

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Recognition of weak interactions in porous supramolecular architectures

Silvia Bracco, Angiolina Comotti, Mario Beretta, Gaetano Distefano, Piero Sozzani. *Department of Materials Science, University of Milano Bicocca, Milan (Italy).* E-mail: silvia.bracco@mater.unimib.it

Nanoporous molecular crystals are attracting large attention in the recent literature for their applications in the field of gas storage, selective recognition and molecular confinement.

We could obtain empty-pore hexagonal crystalline structures held together by weakly directional interactions and fabricate supramolecular architectures that cooperatively stabilizes gases or polymers confined in one-dimensional spaces [1].

Multinuclear NMR of the solid and the gas phase is a method of choice for characterizing nanostructured materials, the size and the shape of the cavities, and their interfaces. The recognition of CH···π specific interactions that contribute to the overall stabilization is demonstrated by the diamagnetic susceptibility effect of the host aromatic ring currents exerted on the guest molecules and by 2D advanced NMR techniques, which provide highly resolved spectra in hydrogen, carbon and phosphorous dimensions [1]. This multinuclear approach allows a detailed description of the role of weak interactions cooperating to fabricate nanostructured materials that exhibit exceptional thermal stability. The large upfield shift provided a tool for understanding the topology of gases or polymer chains interacting with the inner surface of the porous host [2]. For example, we have demonstrated that flexible polymer chains and suitable aromatic host self-assemble in varied ratios to fabricate crystalline and semi-crystalline materials with robust architectures. The high melting macromolecular adducts were successfully prepared by solvent-free mechanochemical or thermal treatment of the crystalline host and few polymers [3]. This unconventional strategy has been applied for the selective confinement of copolymer sequences in the aromatic host, creating novel architectures composed by alternated crystalline lamellae and amorphous layers. In this case the driving force for the fabrication of the nanostructured materials was based on the establishment of a network of cooperative noncovalent intermolecular interactions between the host and some sequences of the copolymer, while steric effects prevent the formation of the inclusion-crystal with the remaining blocks [4].

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Guest Tunable Structure and Magnetism in a Porous Coordination Polymer Followed by parallel In Situ single crystal and powder diffraction

Suzanne Neville,[a] Keith Murray,[a] Cameron Kepert,[b] Gregory Halder[c] Karena Chapman,[c] [a]*School of Chemistry, Monash University, Australia.* [b]*School of Chemistry, University of Sydney, (Australia).* [c]*Advanced Photon Source, IL, (USA).* E-mail: suzanne.neville@monash.edu

Developing functional materials with physical properties that can be controlled on the molecular level is an important goal for the realization of nanoscale devices. Spin crossover (SCO) materials, which show dramatic switching response to external perturbations, e.g. temperature, pressure, light and guest/chemical environment, are excellent candidates. Indeed, we have shown that in the nanoporous two-dimensional network material $[Fe(bpbd)_2(NCS)_2]$.(guest) (bpbd = 2,3-bis(4'-pyridyl)-2,3-butanediol, guest = acetonitrile, acetone,