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Organoboronic Acids as Co-formers in Pharmaceutical Crystal Engineering

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INTRODUCTION & AIM

The ability to predict non-covalent interactions is a major driving force behind the development of multi-component crystals of pharmaceutical compounds. Organoboronic acids have a distinctive hydrogen bonding profile, but their potential as co-formers of a variety of different active pharmaceutical ingredients is still an area of active research. This current work is dedicated to the supramolecular potential of a selection of different boronic acid derivatives as potential tools in the creation of new crystalline forms.

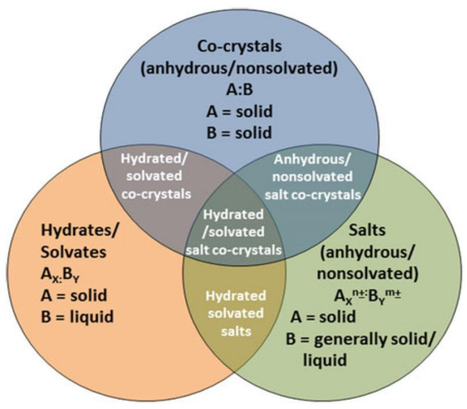

Fig. 1 Major types of crystalline forms: solvates, cocrystals, and salts. Almarsson et al.

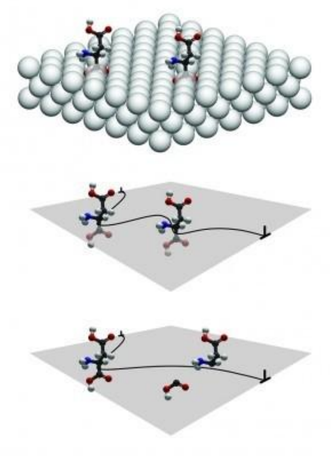

Fig. 2 Crystal engineering based on weak interactions - hydrogen bonds (adapted from literature).

The design of new crystalline architectures relies on the mastery of weak intermolecular interactions. Among these, hydrogen bonds are the most critical due to their strength and directionality, allowing for the precise spatial arrangement of molecules (as illustrated in Figure 2).

METHOD

To evaluate the potential of organoboronic acids as pharmaceutical co-formers, a multi-step experimental and computational approach was employed:

- **Co-crystallization Screening:** A series of experiments were conducted using various active pharmaceutical ingredients (APIs) and selected organoboron derivatives, including phenylboronic acid and its substituted analogs.
- **Crystallization Techniques:** The synthesis of new multi-component phases was attempted via solution-based slow evaporation and liquid-assisted grinding (LAG**)** from organic solvents.
- **CSD Data Mining:** A systematic analysis of the **Cambridge Structural Database (CSD)** was performed to elucidate the molecular assembly processes. The study focused on the competitive interplay between homosynthons (self-association) and heterosynthons (intermolecular recognition) within boronic acid-based systems (see Figure 3).

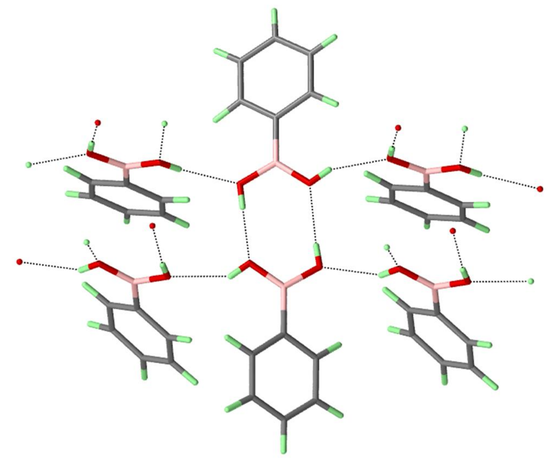

Fig. 3 Phenylboronic acid crystallizes in the orthorhombic space group *Iba2*. Each asymmetric unit consists of two independent molecules linked via a double O–H...O hydrogen bond.

RESULTS & DISCUSSION

The results demonstrate the prevalence of strong self-associating motifs within boronic acids that can significantly impact the API-co-former interplay (Figure 4). The findings indicate that specific steric and electronic characteristics of the organic boronic acid compounds under investigation affect the lattice stability (Figures 6 and 7). The study provides a structural rationale for the observed crystallization behavior, emphasizing the role of synthon competition in the design of pharmaceutical co-crystals (see Figures 4–7).

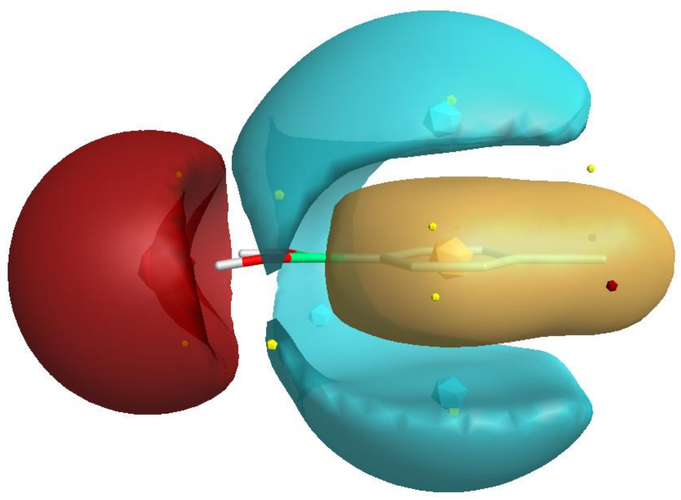

Figure 4. 4-chlorophenylboronic acid: Red highlights a potential hydrogen bond interaction, yellow represents the hydrophobic moiety, and blue indicates a negative pi-charge.

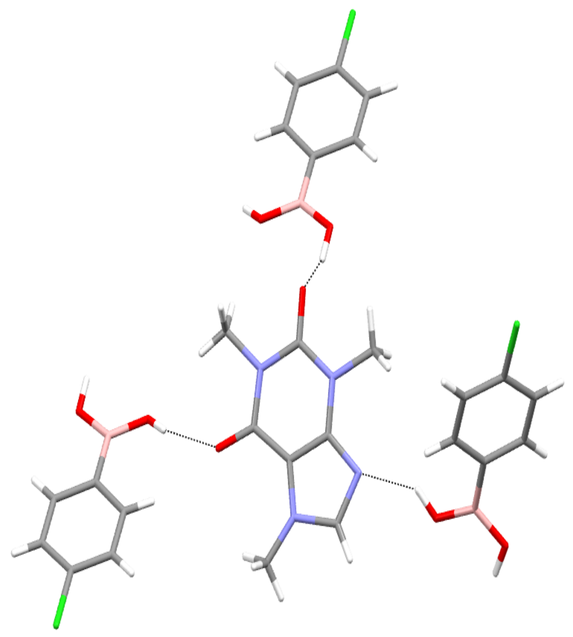

Figure 5. Observed interactions between caffeine and 4-chlorophenylboronic acid.

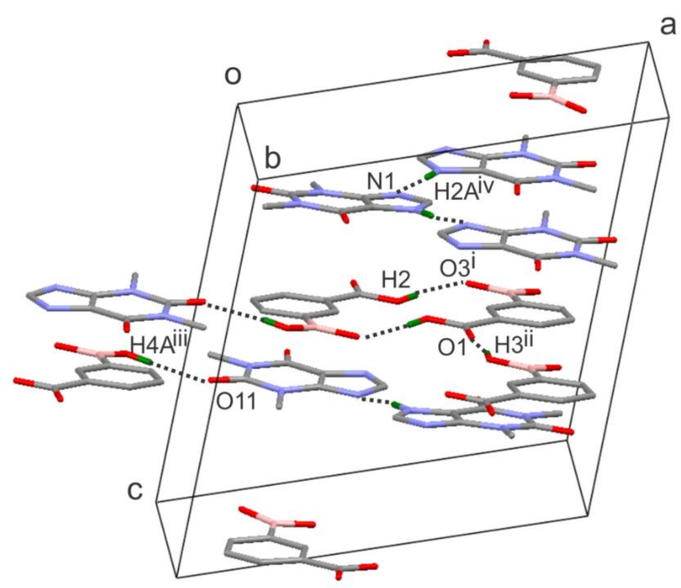

Figure 6. Weak intermolecular interactions between theophylline and 3-carboxyphenylboronic acid

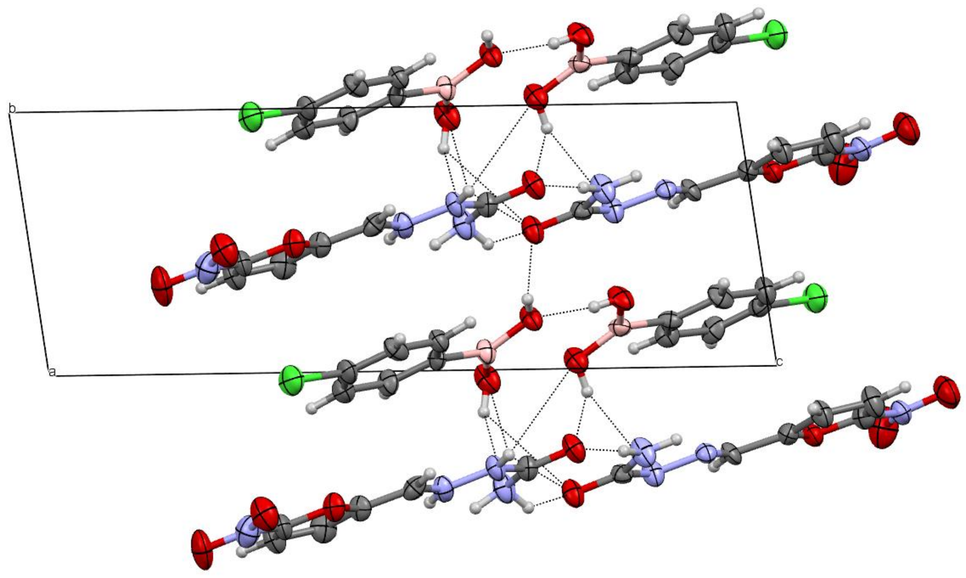

Figure 7. Structural analysis of the nitrofurazone – 4-chlorophenylboronic acid co-crystal: boronic–boronic, nitrofurazone–nitrofurazone, and boronic–nitrofurazone interactions.

CONCLUSIONS

The work provides critical insights into the crystal engineering process mediated by boronic acids and serves to clarify the structural requirements for successful supramolecular synthesis. These results are essential for refining the selection criteria used to identify co-formers in future attempts to optimize the crystallization conditions of new multicomponent pharmaceutical phases.

FUTURE WORK/ REFERENCES/ACKNOWLEDGMENT

1. Almarsson, Ö.; Zaworotko, M. J. Crystal engineering of the composition of pharmaceutical phases. Chem. Commun. 2004, 1889–1896.