

# Combined Use of Structure Analysis, Studies of Molecular Association in Solution, and Molecular Modelling to Understand the Different Propensities of Dihydroxybenzoic Acids to Form Solid Phases

**Aija Trimdale-Deksne, Agris Bērziņš**  
aija.trimdale@lu.lv

University of Latvia Faculty of Chemistry,  
Jelgava street 1, Riga, Latvia



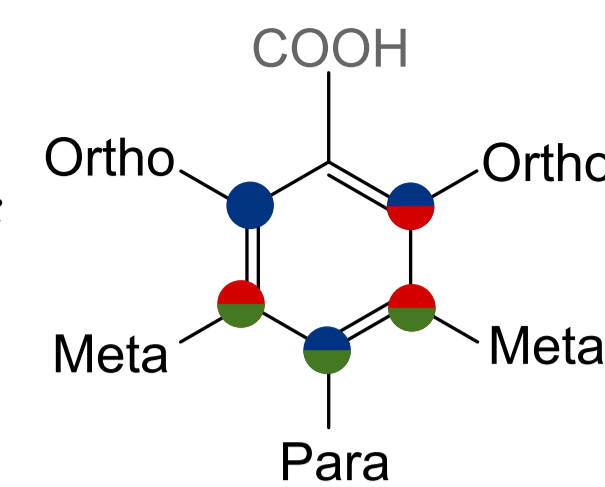
Dihydroxybenzoic acids (diOHBA) are small organic molecules. Arrangement of OH groups in the benzene ring has a significant effect on their propensity to form different solid phases<sup>1-8</sup> when crystallized from solution – according to solid phases obtained from acetonitrile (ACN) and 2-propanol (IPA), all six diOHBA were categorise into four distinctive groups – Group A, B, C and D.

To determine the possible mechanism how the positions of the phenolic hydroxyl groups affect the diversity of solid phases formed by the diOHBA, a combined study using structure analysis, studies of molecular association in solution<sup>9</sup>, electrostatic potential calculations and molecular dynamic simulations<sup>10</sup> was performed.

## Summary

- Intramolecular bond O2...H-O3 (in ortho-substituted diOHBA) was identified as the most influential on a) involvement of phenolic OH groups in self-association and solvent-solute association processes and b) on the distribution of ESP extrema in the molecule. This coincides with Group A and B diOHBA showing less pronounced solvate formation prosperity.
- In the case of Group C (2,6-diOHBA), two intramolecular bonds formed by the carboxylic group and syn-anti conformers in the solution make it highly different from the rest of the diOHBA.
- Studies of association in solution demonstrated that the observed higher abundance of OH group associates can be linked to a higher solvate formation propensity (as exhibited by non-ortho-diOHBA).
- Additionally, the non-ortho-substituted diOHBA have an even distribution of ESP extrema, resulting in the formation of intermolecular interactions, allowing for the incorporation of guestmolecules.
- The absence of notable O1...O2 self-associate formation in solution indicates that the formation of R<sup>2</sup><sub>2</sub>(8) in solid-state is not caused by its presence in solution.

- Group A** – 2,3-diOHBA, only one polymorphic form was obtained;
- Group B** – 2,4-, 2,5-diOHBA, mostly the most stable polymorph was obtained;
- Group C** – 2,6-diOHBA, prone to form hydrate but no solvates with given solvents;
- Group D** – 3,4-, 3,5-diOHBA, extensively form hydrates and solvates.

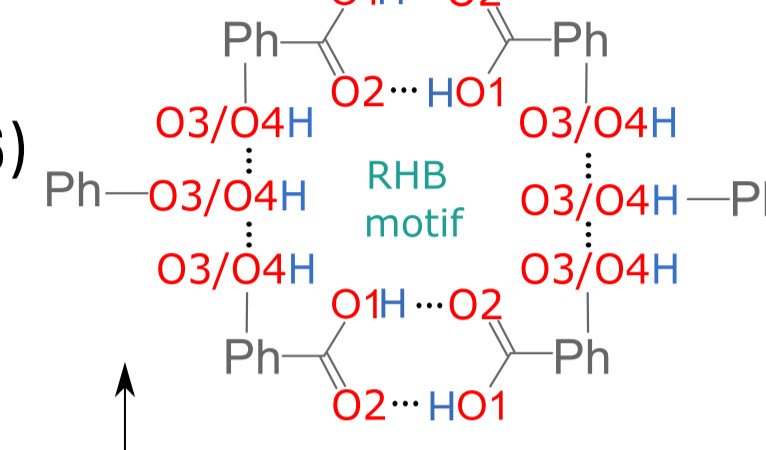
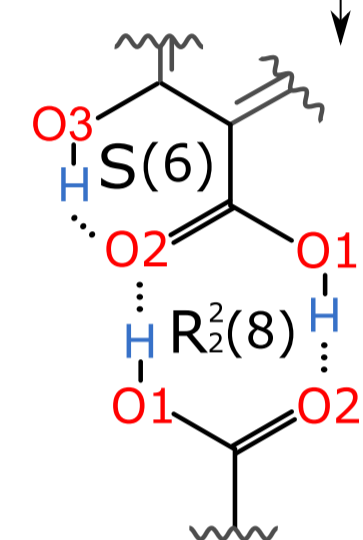


## Crystal structure analysis

Analysis of hydrogen bond motifs in crystal structures of nonsolvated, hydrated and solvated forms.

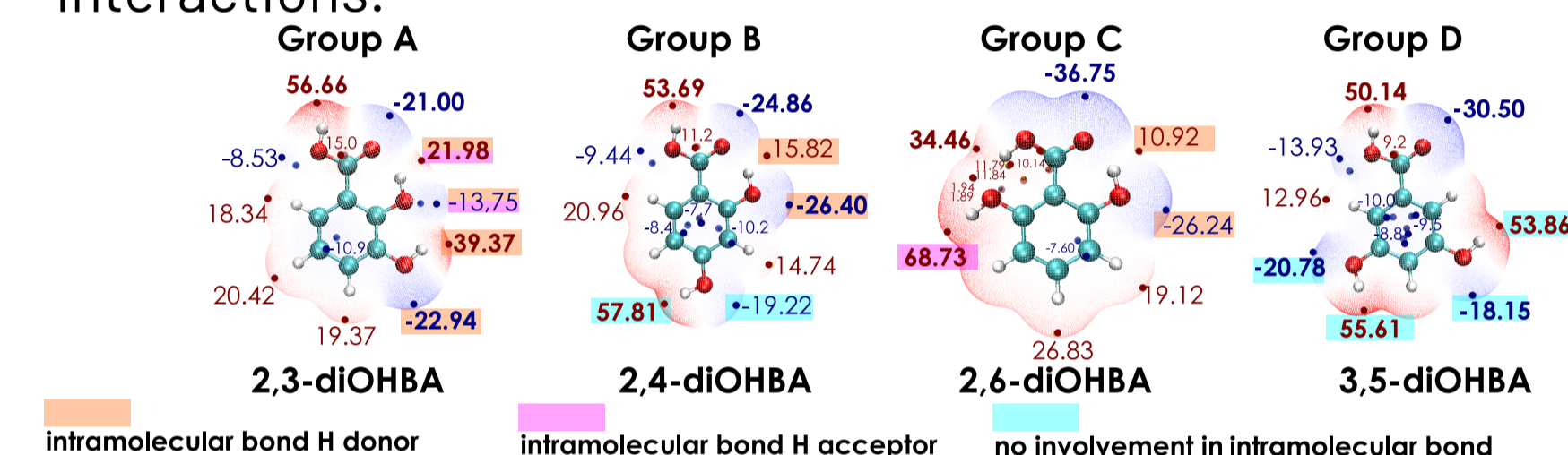
- The main hydrogen bond motif – intramolecular hydrogen bond S(6)
- Equally common motif – carboxyl acid homodimers R<sup>2</sup><sub>2</sub>(8), absent only in few Group C and D structures.
- Non-solvate phases containing R<sup>2</sup><sub>2</sub>(8) nearly always contained ring-like hydrogen bond motifs (RHB motifs) formed by 6 molecules\*.
- Common occurrence – layered structure formed by R<sup>2</sup><sub>2</sub>(8) dimers or even RHB motifs that are interconnected by π...π interactions.

\*Non-solvated forms without RHB motif can be obtained from specific solvents (2,3-diOHBA II), in specific conditions (2,6-diOHBA I) or in experiments other than solution crystallization (3,5-diOHBA II).

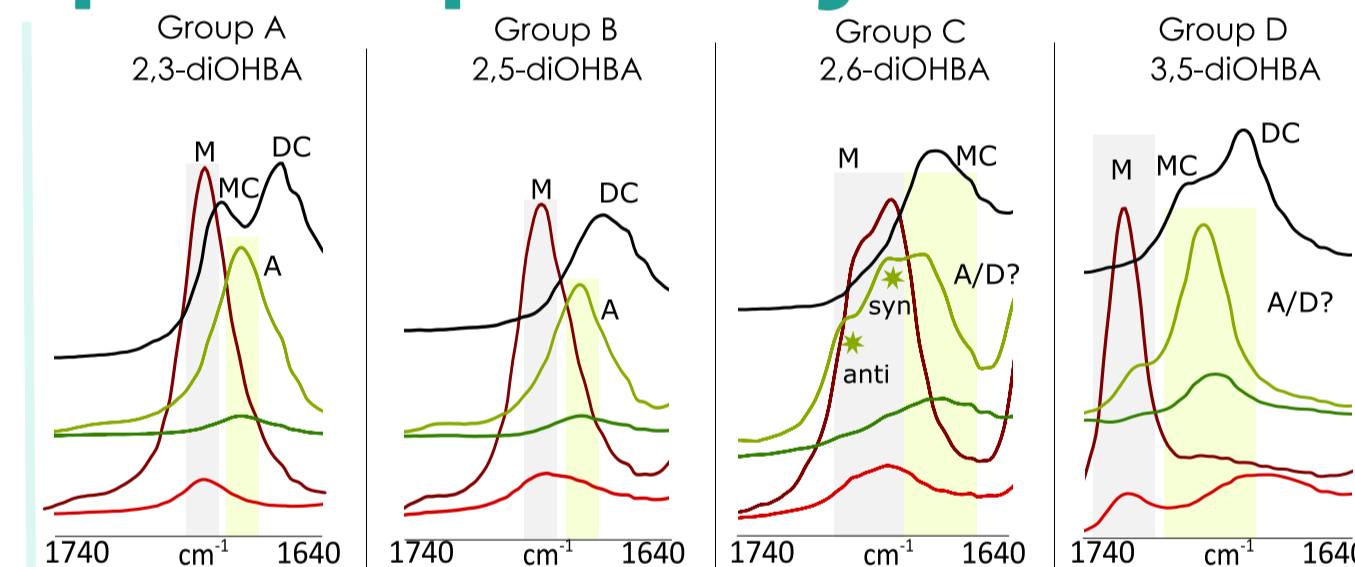


## ESP surfaces

- For all ortho-substituted diOHBA (Group A-C), at least one OH group forms intramolecular hydrogen bond with COOH group, thus the positive extrema of ESP are not evenly distributed across the molecule.
- Group D diOHBA ESP extrema values on OH and COOH groups does not significantly differ from each other and are evenly distributed across the molecule.
- Group D diOHBA ESP extrema values on COOH group are lower than in other syn-diOHBA (Group A,B), indicating on different affinity towards formation of intermolecular interactions.

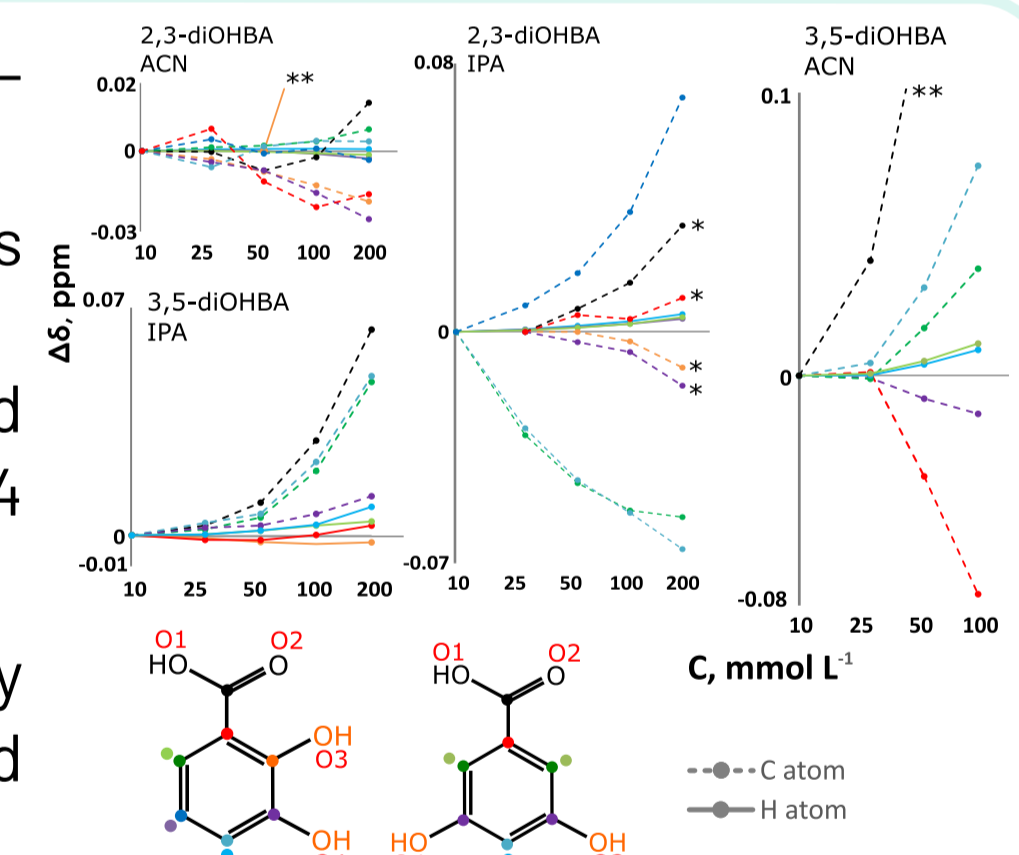


## Spectroscopic investigations



Only C=O (O2) region investigated in FT-IR.  
C – in crystal structure  
M – monomer  
D – carboxylic acid homodimer  
A – associates involving O2  
\* – 2,6-diOHBA conformers

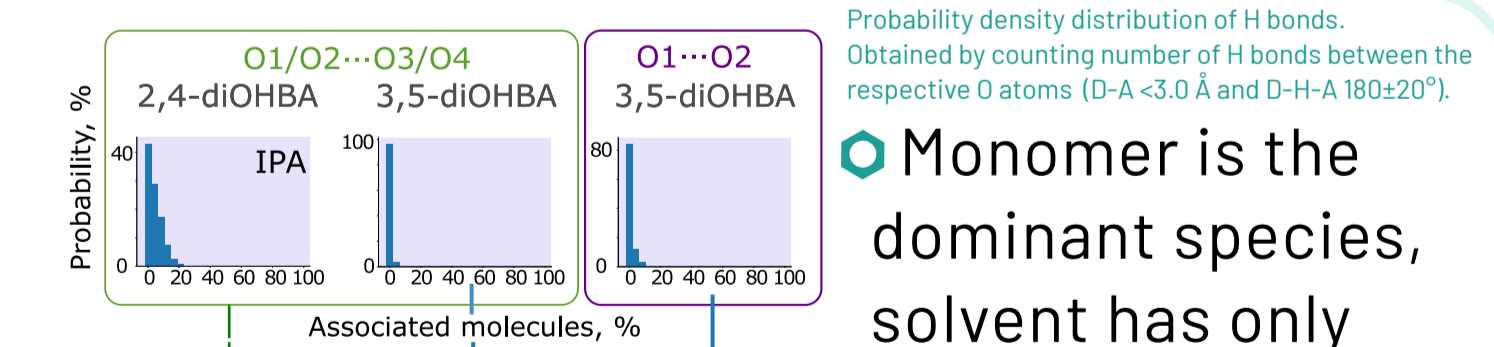
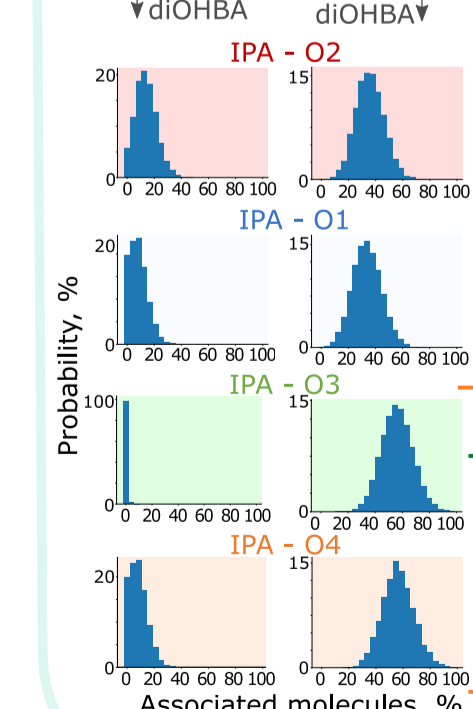
- In IPA solution all diOHBA experience self-association.
- In ACN solution only Group D compounds formed O2 atom involving associates.
- Most probable self-associates are formed by O2...O1 (COOH...COOH) and/or O2...O3/O4 (C=O...OH) hydrogen bonds.
- Overall, obtained spectra indicate that only Group D compounds experience pronounced self-association in solution.



## Molecular dynamic simulations

Simulation box represents ~0.15 M solutions in ACN and IPA.

- If possible, diOHBA O atoms form hydrogen bonds with solvent molecules, solvent mostly act as H bond acceptor.
- Intramolecular bond O2...H-O3 slightly reduces formation of O2...H<sub>solv</sub> bond and heavily affects O3-H...O<sub>solv</sub> bond.
- Formation of O3/O4-H...O<sub>solv</sub> bond is considerably higher for Group D than for ortho-substituted diOHBA.
- Intramolecular bond between the phenolic OH groups slightly affects only the hydrogen bond donor behaviour.



- Monomer is the dominant species, solvent has only minor effect
- Ortho-substituted diOHBA: the most common are O1/O2...O3/O4 self-associates.
- Group D: formation of O1/O2...O3/O4 associates is negligible, more common are O1...O2 associates.

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