

Combined use of structure analysis, studies of molecular association in solution and molecular modelling to understand the different propensity of dihydroxybenzoic acids to form solid phases

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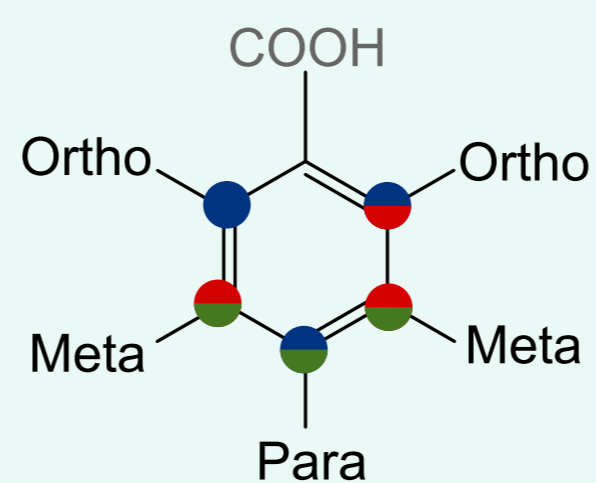
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Dihydroxybenzoic acids (diOHBA) are small organic molecules. Arrangement of OH groups in the benzene ring has a significant effect on their propensity to form different solid phases¹⁻⁸ when crystallized from solution – according to solid phases obtained from acetonitrile (ACN) and 2-propanol (IPA), all six diOHBA were categorised 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 solution⁹, electrostatic potential calculations and molecular dynamic simulations¹⁰ was performed.

- 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.



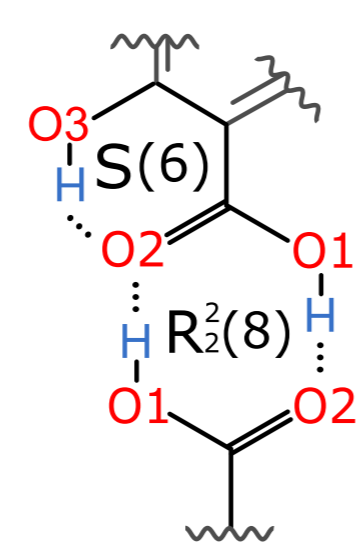
An easily noticeable link between OH group position and solvate formation propensity in the studied solvents:

- (+)** No OH groups in ortho position, readily forms multiple solvated forms (3,4- and 3,5-diOHBA);
- (+)** Do not show propensity to form any solvated phases in the studied solvents (2,3- and 2,5-diOHBA);
- (+)** Hydrates can be achieved (2,4- and 2,6-diOHBA).

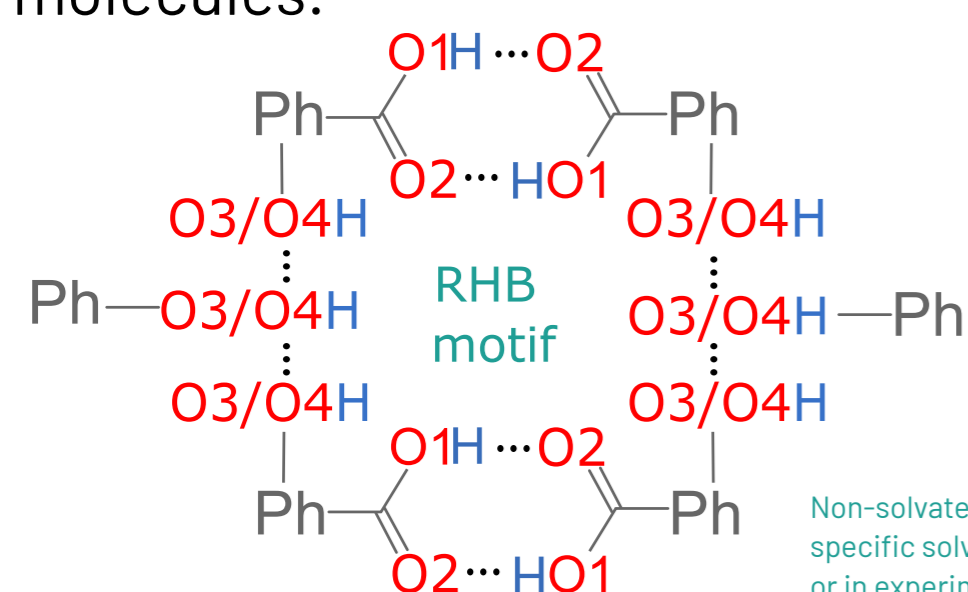
Crystal structure analysis

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

- The main hydrogen bond motif – intramolecular hydrogen bond S(6)
- Equally common motif – carboxylic acid homodimers R₂²(8), absent only in few Group C and D structures.
- Non-solvate phases containing R₂²(8) nearly always contained ring-like hydrogen bond motifs (RHB motifs) formed by 6 molecules.

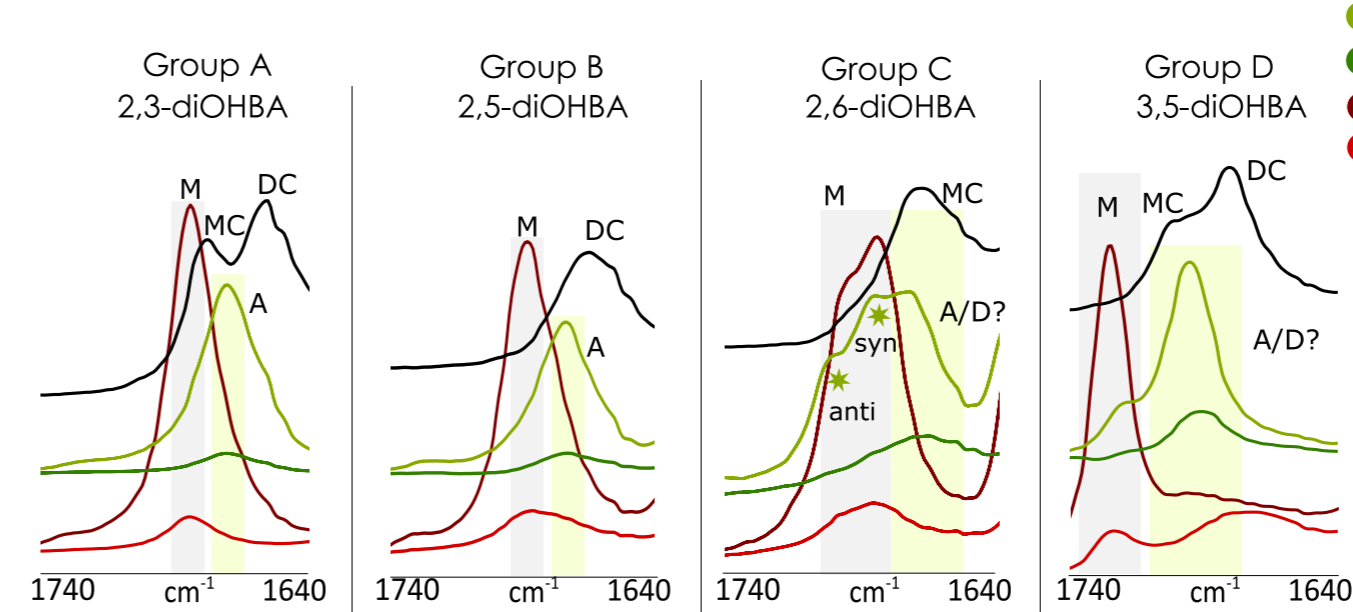


- Common occurrence – layered structure formed by R₂²(8) dimers or even RHB motifs that are interconnected by π...π interactions.



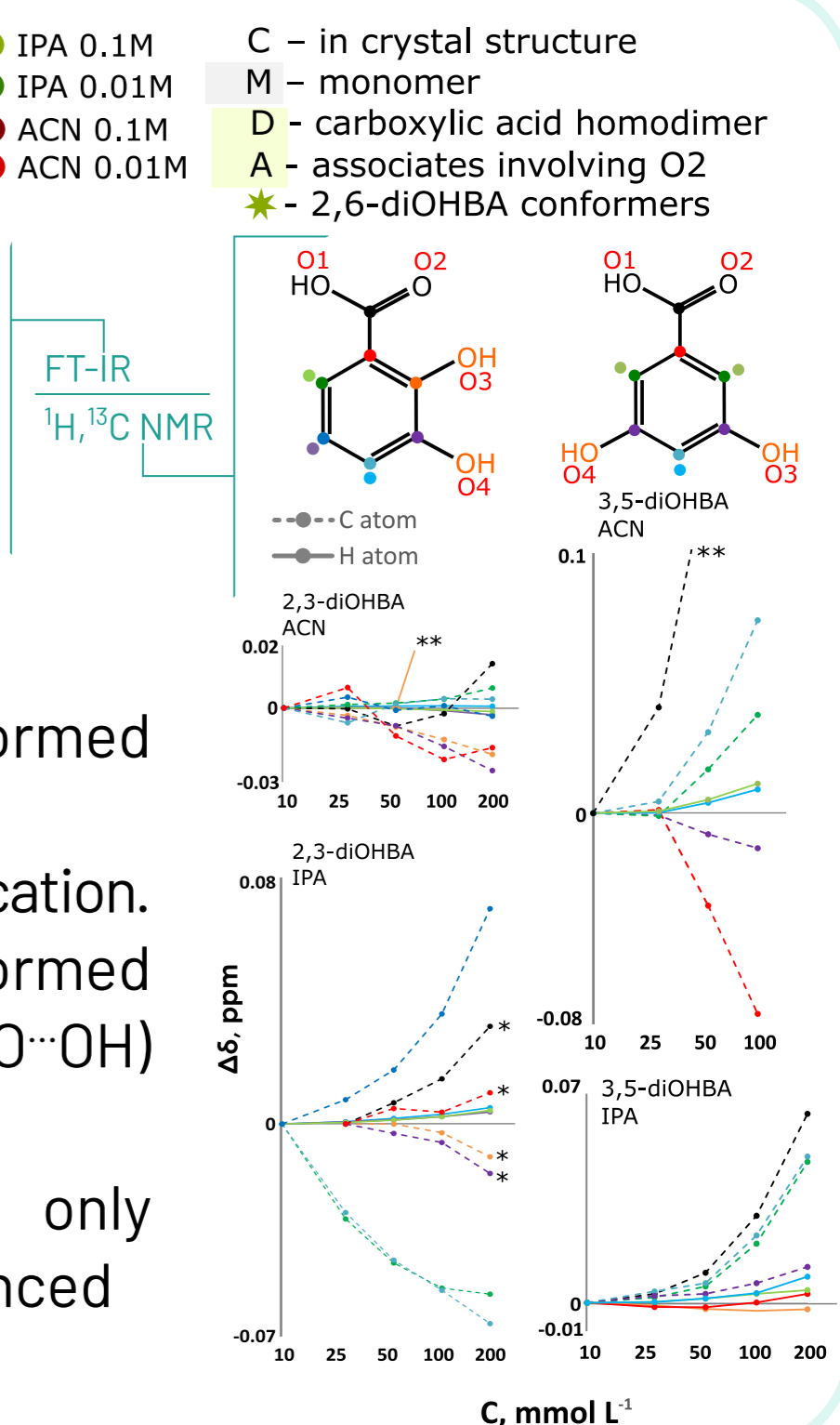
Non-solvated forms without RHB motif can be obtained from specific solvents (2,3-diOHBA II), in specific conditions (2,6-diOHBA I) or in experiments other than solution crystallization (3,5-diOHBA II).

Spectroscopic investigations

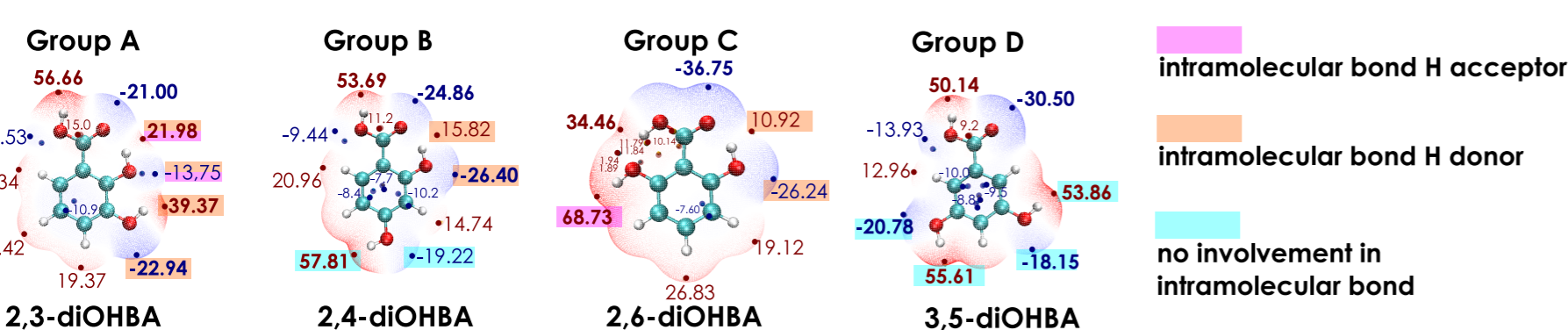


Only C=O (O2) region investigated in FT-IR.

- In ACN solution only Group D compounds formed O2 atom involving associates.
- In IPA solution all diOHBA experience self-association.
- 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.



ESP surfaces

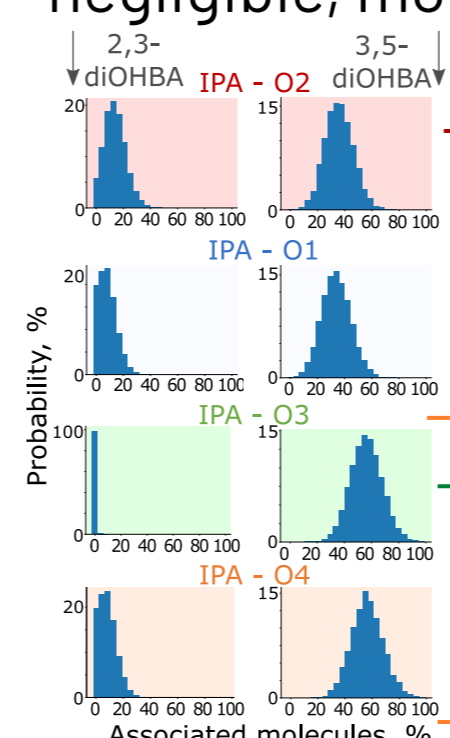


- For all ortho-substituted diOHBA (Group A-C), at least one OH group forms intramolecular hydrogen bond with COOH group, thus the positive extrema of ESP are not evenly distributed across the molecule.
- Group D diOHBA ESP extrema values on OH and COOH groups does not significantly differ from each 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.

Molecular dynamic simulations

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

- Monomer is the dominant species and solvent has a minor effect.
- diOHBA express π...π interactions resembling those found in crystal structures.
- 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.



- 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_{solv} bond and heavily affects O3-H...O_{solv} bond.
- Formation of O3/O4-H...O_{solv} 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.

Summary

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.

The absence of notable O1...O2 self-associate formation in solution indicates that the formation of R₂²(8) in solid-state is not caused by its presence in solution. However, the more desired is O1...O2 associate formation over O1/O2...O3/O4 associate formation in solution, the more prominent is diOHBA solvate formation propensity.

Acknowledgements

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Solute-solvent association processes with IPA cannot be directly linked to solvate formation (there are no known IPA solvates). However, prominent association processes at phenolic OH groups in general can be linked to higher solvate formation propensity.

Intramolecular bond O2...H-O3 found in all 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 propensity.

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