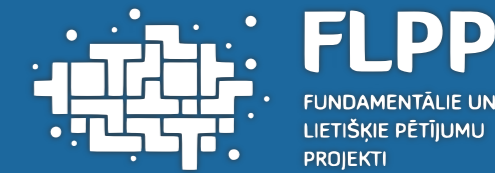


Use of Molecular Dynamics Simulations to Investigate the Molecular Association of Dihydroxybenzoic Acids in Solution

Aija Trimdale, Agris Bērziņš
ajja.trimdale@lu.lv



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



UNIVERSITY OF LATVIA



UNIVERSITY OF LATVIA
Laboratory of
Molecular Crystals

Molecular dynamics (MD) is a very versatile method that can depict the motion of the molecular system. It can be used in association studies in solution^{1,2} for small organic molecules such as dihydroxybenzoic acids (diOHBA) – six isomeric molecules with mutually different ability to form solvated and polymorphic forms³⁻⁶.

In the previous computational studies⁷ no distinctive tendencies for formation of carboxyl acid homodimer (present in almost all crystal structures) in solution was observed. However, calculations indicated towards existence of possible stable hydrogen bond associates with solvent molecules.

In this study, diOHBA isomers having different diversity of obtainable crystalline phases (2,3-, 2,4-, 3,4- and 3,5-diOHBA) and 2-propanol (IPA) as a solvent that can act both as hydrogen bond donor and acceptor and did not form solvate were used.

MD simulations for diOHBA IPA solutions were used to investigate molecular association processes and rationalize how these processes differed for each diOHBA and could influence obtainable crystalline phase. In addition, FT-IR spectroscopy (C=O antisymmetric stretch region) was used to experimentally confirm/deny the formation of associates observed in the simulations.

	2,3-diOHBA	2,4-diOHBA	3,4-diOHBA	3,5-diOHBA
Tendencies in solid phase formation	Almost only most stable form I is obtained.	Mostly only most stable form II is obtained, forms hemihydrate.	Prone to form 2 monohydrates, form solvates. Only 1 polymorph.	Prone to both solvate and hydrate formation. Forms mixed solvates.
Solid phase obtained from IPA	Form I	Form II	Form I	Form I + hemihydrate
Probability of hydrogen bond associates with IPA				
Probability of self-association (donor-acceptor distance between O atoms < 3.0 Å and angle cutoff set at 20°)				
	<p>Visual observations from simulation: π-π stacking, trimerisation (involving COOH group), clustering (>3 molecules).</p>	<p>Visual observations from simulation: Mostly COOH-OH and COOH-CO-OH dimers.</p>	<p>Visual observations from simulation: almost no self-association.</p>	<p>Visual observations from simulation: almost no self-association.</p>
FT-IR	<p>Free energy profile of self-associated diOHBA dimers in solutions. Clusters. M, MC, DC.</p>	<p>Free energy profile of self-associated diOHBA dimers in solutions. Both mentioned associates and associate with IPA. M, DC.</p>	<p>Free energy profile of self-associated diOHBA dimers in solutions. Associates with IPA. M, DC, A/D?</p>	<p>Free energy profile of self-associated diOHBA dimers in solutions. Associates with IPA. M, MC, DC, A/D?</p>
● solid ● IPA 0.1M ● IPA 0.01M M - monomer D - carboxyl acid homodimer A - associate XC - in crystal structure	<ul style="list-style-type: none"> ● Only compound that do not express diversity of solid phases. ● Both intramolecular bonds heavily affects formation of associates. ● Only compound showing strong self-association as clustering and π-π stacking. ● Some trimers represent motifs present in crystal structure (form I). ● Overall, no tendencies towards formation of associates with IPA. 	<ul style="list-style-type: none"> ● Only compound forming hydrogen bond dimers involving carboxyl group. ● In addition, also forms hydrogen bond associates with IPA - Prefers interact with IPA via free 4OH.p ● Self-association prevents from formation of solvated phases. 	<ul style="list-style-type: none"> ● Formation of monohydrates and solvated phases are more frequent than unsolvated form. ● Almost all molecules are involved into at least one hydrogen bond with IPA. ● Compound shows almost no self-association. ● Absence of self-associates and pronounced hydrogen bond formation with IPA causes formation of solvated phases. 	<ul style="list-style-type: none"> ● Obtaining of unsolvated form is challenging. ● Solvated phases are almost always obtained when crystallized form solutin. ● Absence of intramolecular bond - both hydroxyl groups forms hydrogen bond with IPA. ● All molecules are involved into multiple hydrogen bond with IPA. ● Compound shows almost no self-association. ● Absence of self-associates and pronounced hydrogen bond formation with IPA causes formation of solvated phases.

Conclusions

- Presence of intramolecular bonds (as in ortho-substituted diOHBA and with neighboring hydroxyl groups) hinders association with IPA (solvent) molecules thus also hinders formation of solvated forms.
- Pronounced self-association promotes formation of unsolvated phases. Furthermore, if hydrogen bond motif in solution resemble those present in crystal structure, more likely formation of specific will be observed.
- The more freely molecule can form hydrogen bonds with IPA (solvent) molecules the more pronounced solvate former the compound is.

Acknowledgements

This research has been supported by the Latvian Council of Science, project "Crystal engineering of pharmaceutical multicomponent phases for more efficient crystalline phase design", project No. lzp-2018/1-0312.4

Presented at MSAC 2020 October 23th 2020 in Riga

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