Computational Study of Association of Dihydroxybenzoic Acids in Solution:

Testing the Molecular Self-Association Computational Methodology for Formation of Binary Systems

Aija Trimdale, Agris Bērziņš
aija.trimdale@lu.lv
University of Latvia Faculty of Chemistry, Jelgava street 1, Riga, Latvia

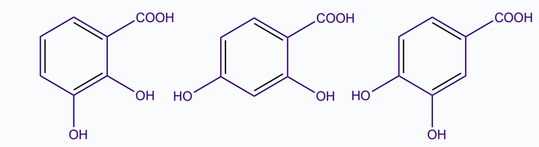
UNIVERSITY OF LATVIA ANNO 1919

FLPP FUNDAMENTĀLIE UN LIETIŠĶIE PĒTĪJUMU PROJEKTI

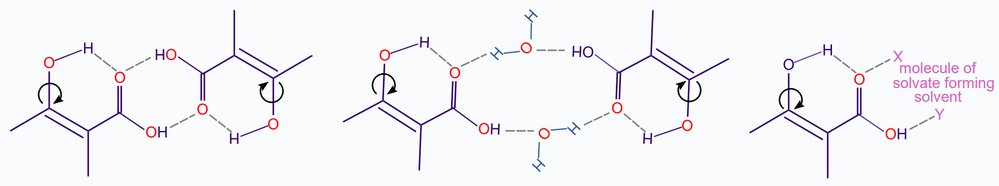
Introduction & aim

Dihydroxybenzoic acids (diOHBA) are small organic molecules that form variety of polymorphs, solvates & hydrates [1,2,3].
In this study three isomers were used – 2,3-diOHBA, 2,4-diOHBA and 3,4-diOHBA.

Main hydrogen bond motif in OHBA found in CSD structures is dimer although, other motifs also exist: heterotetramers with water (CSD refcode DIWNON01) and associate with solvent molecule (CSD refcode GUTNOY)).



To evaluate the likelihood of existence of such motifs in solutions of diOHBA, already validated computational approach for molecular self-association and dimerization in solution [4,5] was used. This also allows to test if application of given methodology is possible in other situations than the dimerization



Homodimers & heterotetramers with water

ΔG of association of homodimers and heterotetramers with two water molecules formed by different conformers in gas phase and multiple solvents were calculated:

Conformation	2,3-diOHBA C1	C2	C3	C4	2,4-diOHBA C1	C2	C3	C4	3,4 diOHBA Z1	Z2
Environment	Homodimers, ΔG assoc , kJ/mol									
vacuum	-17.4	**-32.6**	-18.5	-18.8	-17.3	**-34.7**	-24.5	-21.5	**-28.6**	-25.2
water	1.5	**-3.8**	7.2	3.0	4.9	**-5.4**	1.9	1.5	1.0	**-0.3**
ACN	-2.9	**-12.1**	-2.7	-6.0	-2.5	**-15.7**	-10.0	-9.1	-10.2	**-10.9**
DXN	-15.2	**-27.7**	-15.5	-16.9	-15.0	**-30.3**	-21.6	-22.7	**-33.3**	-22.7
Acetone	-4.5	**-13.9**	-4.6	-7.6	-4.2	**-17.7**	-11.0	-10.6	-12.0	**-12.2**
DMSO	-5.8	–	–	–	-5.6	–	–	–	-13.3	–
DMA	-5.4	–	–	–	-5.2	–	–	–	-12.9	–
AcOH	-5.7	–	–	–	-3.7	–	–	–	-9.7	–
	Heterotetramers with water, ΔG assoc, kJ/mol									
vacuum	0.5	203	5.8	5.0	2.9	**-2.4**	-2.0	4.4	**-19.1**	–
water	34.8	268	47.5	47.6	38.8	47.0	39.9	48.2	34.1	–
ACN	212	401	237	227	203	195	257	255	221	–
DXN	**-2.0**	209	5.5	3.5	0.7	-1.1	**-2.2**	0.09	**-16.6**	–
Acetone	17.5	241	26.5	25.6	20.1	24.2	18.9	25.3	9.1	–

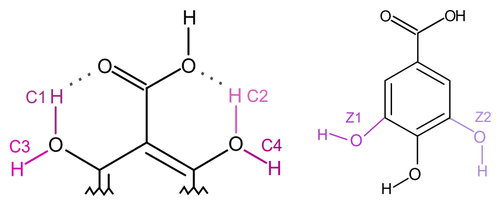
- For homodimers $\Delta G_{assoc}>0$ only in water.
- Most stable conformation in solution **(most negative ΔG_{assoc})** is C2.

- For heterotetramers in almost all cases $\Delta G_{assoc}>0$.
- ΔG_{assoc} for the corresponding homodimers are notably lower – in water diOHBA are more prone to form dimer.

Associates between COOH group and solvent

ΔG_{assoc} of associates with solvent molecule involving only diOHBA's COOH group and C1 conformation in gas phase and multiple solvents (that do not form solvate) were calculated:

Solvent molecule in associate	2,3-diOHBA DXN	DMSO	DMA	AcOH	2,4-diOHBA DXN	DMSO	DMA	AcOH	3,4 diOHBA DXN	DMSO	DMA	AcOH
Environment	Associates ΔG_{assoc},kJ/mol and comparison to homodimers											
vacuum	-20.8	-26.6	-10.1	-21.3	-20.4	-24.8	-8.7	-20.7	-30.7	-36.9	-20.3	-36.6
C1(Z1)/min	A/D	A/D	D/D	A/D	A/D	A/D	D/D	A/D	A	A	D	A
ACN	-17.2	-12.5	-5.7	-11.8	-16.5	-9.6	-3.6	-5.8	-18.4	-12.6	-1.8	-13.9
C1(Z1)/min	A/A	A/A	A/D	A/D	A/A	A/D	A/D	A/D	A/A	A/A	D/D	A/A
Acetone	-30.0	-20.5	-14.1	-16.4	-17.1	-10.5	-4.2	-7.5	-20.8	-14.4	-3.7	-17.5
C1(Z1)/min	A/A	A/A	A/A	A/A	A/D	A/D	D/D	A/D	A/A	A/A	D/D	A/A
Own sol. C1(Z1)	-40.3 A	-21.2 A	-14.4 A	-11.3 A	6.6 D	-6.2 A	-5.8 A	36.6 D	-29.8 D	-15.1 A	-3.7 D	-13.1 A



Conformations involving:
- rotation of COOH and ortho-OH group (C1, C2, C3, C4)
- rotation of only COOH group (Z1, Z2).

All dimers in CSD stuctures correspond to C1, Z1.

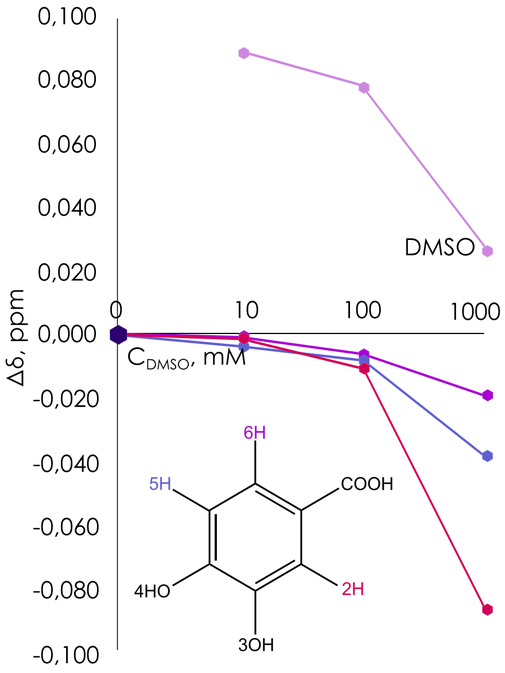
- In almost all cases $\Delta G_{assoc}<0$ – associates are stable.
- If $\Delta G_{assoc,\ associate} < \Delta G_{assoc,\ homodimer}$, associate could exist in solution.
- If in coresponding environment $\Delta G_{assoc,\ associate}$ is compared with:
  a) $\Delta G_{assoc,\ C1(Z1)\ homodimer}$ – in most cases A is more stabile.
  Except: DMA associates and in associate forming medium.
  b) $\Delta G_{assoc,\ minimum\ energy\ homodimer}$ – in more cases D is more stable.
  Particularly for 2,4-diOHBA.
- Results suggests that such associates could exist in solution.

Summary

- Used computational methodology for self-association in solutions can be successfully used in other studies regarding association in solution.
- Comparison of ΔG_{assoc} of corresponding homodimers and heterotetramers shows that in water diOHBA are more prone to form dimers.
- Results suggested that associates of diOHBA and solvate forming solvent molecule (involving only COOH group) could exist in solution.
- ^{1}H NMR points towards formation of associates involving OH group showing that ΔG_{assoc} of all possible associates in solutions needs to be taken into consideration.

^{1}H NMR spectroscopy & calculations

- Associate formation affects δ as x= f(C)[6].
- C_{diOHBA}=constant, C_{DMSO}–changing. Medium–CD_3CN.
- Δδ<0 – some kind of associate is indeed forming in solution.
- By calculating chemical shieldings and simulating transitions from dimers to associates (involving COOH or OH group) negative Δδ points towards OH-associate.



Presented at MSAC 2019 October 24th 2019 in Riga

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

References
[1] Cryst.Growth Des.,2010, 10,5, 2388-2399.
[2] Chem. Commun., 2011, 47, 5443–5445.
[3] Cryst.Growth Des.,2011, 11,1, 210-220.
[4] CrystEngComm, 2013, 15, 6564–6577.
[5] Phys. Chem. Chem. Phys., 2019, 21, 4258-4267.
[6] CrystEngComm, 2015,17, 5237-5251.