EXPERIMENTAL AND COMPUTATIONAL INVESTIGATION OF SOLID FORM LANDSCAPES OF SEVERAL NITROBENZOIC ACID DERIVATIVES

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IEGULDĪJUMS TAVĀ NĀKOTNĒ

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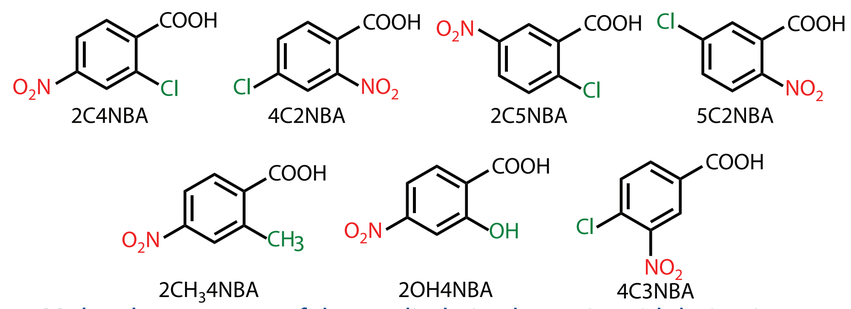
Introduction

Five different isomers of chlorontrobenzoic acid 2C4NBA, 4C2NBA, 2C5NBA, 5C2NBA, and 4C3NBA as well as 2-methyl-4-nitrobenzoic acid $2CH_3$4NBA and 2-hydroxy-4-nitrobenzoic acid 2OH4NBA, see below, were studied experimentally and computationally.



Molecular structure of the studied nitrobenzoic acid derivatives.

Aim

To explore the experimental polymorph and solvate landscape, and try to rationalize:

- The observed differences in appearance of several different polymorphic forms
- The observed differences in propensity to form solvates
- The formation of solvates with particularly the observed solvents

Solid form screening

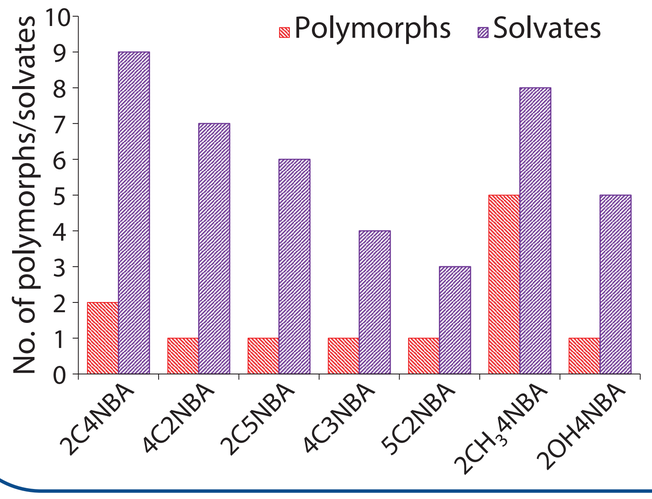
Solid form screening was carried out by crystallizing the selected compounds from multiple solvents having different physicochemical properties (37 for 2C4NBA, 32 for other CNBA isomers and 31 for $2CH_3$4NBA and 2OH4NBA).

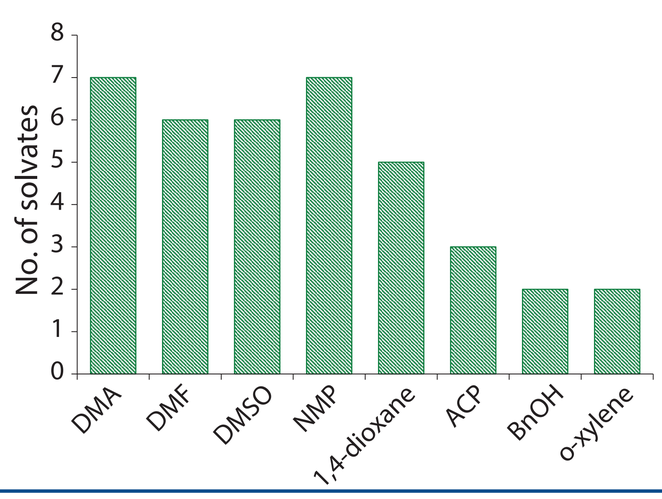
Crystal forms obtained in crystallization of the studied compounds from selected solvents

Solvent	2C4NBA	4C2NBA	2C5NBA	4C3NBA	5C2NBA	$2CH_3$4NBA	2OH4NBA
toluene	I	I	I	I	I	I / S_{TOL}	I
o-xylene	S_{XYL}	I	I	I	I	S_{XYL}	I
Acetophenone	S_{ACP}	S_{ACP}	S_{ACP}	I	I	I	I
DMF	S_{DMF}	S_{DMF}	S_{DMF}	S_{DMF}	I	S_{DMF}	S_{DMF}
DMA	S_{DMA}	S_{DMA}	S_{DMA}	S_{DMA}	S_{DMA}	S_{DMA}	S_{DMA}
DMSO	S_{DMSO}	S_{DMSO}	S_{DMSO}	S_{DMSO}	I	S_{DMSO}	S_{DMSO}
NMP	S_{NMP}	S_{NMP}	S_{NMP}	S_{NMP}	S_{NMP}	S_{NMP}	S_{NMP}
chloroform	I	I	I	I	I	S_{CLF}	I
benzyl alcohol	S_{BA}	I / S_{BA}	I	I	I	I	I
1,4-dioxane	S_{DIOX}	S_{DIOX}	S_{DIOX}	I	S_{DIOX}	I	S_{DIOX}
1,3-dioxolane	I	I	I	I	I	S_{DXLN}	I
water	MH	I	I	I	I	I / II	I
Other solvents	I / II	I	I	I	I	I / II / III / V	I

- All previously described polymorphs and solvates of 2C4NBA as well as structurally characterized ansolvates of 4C2NBA, 2C5NBA and 4C3NBA were obtained.

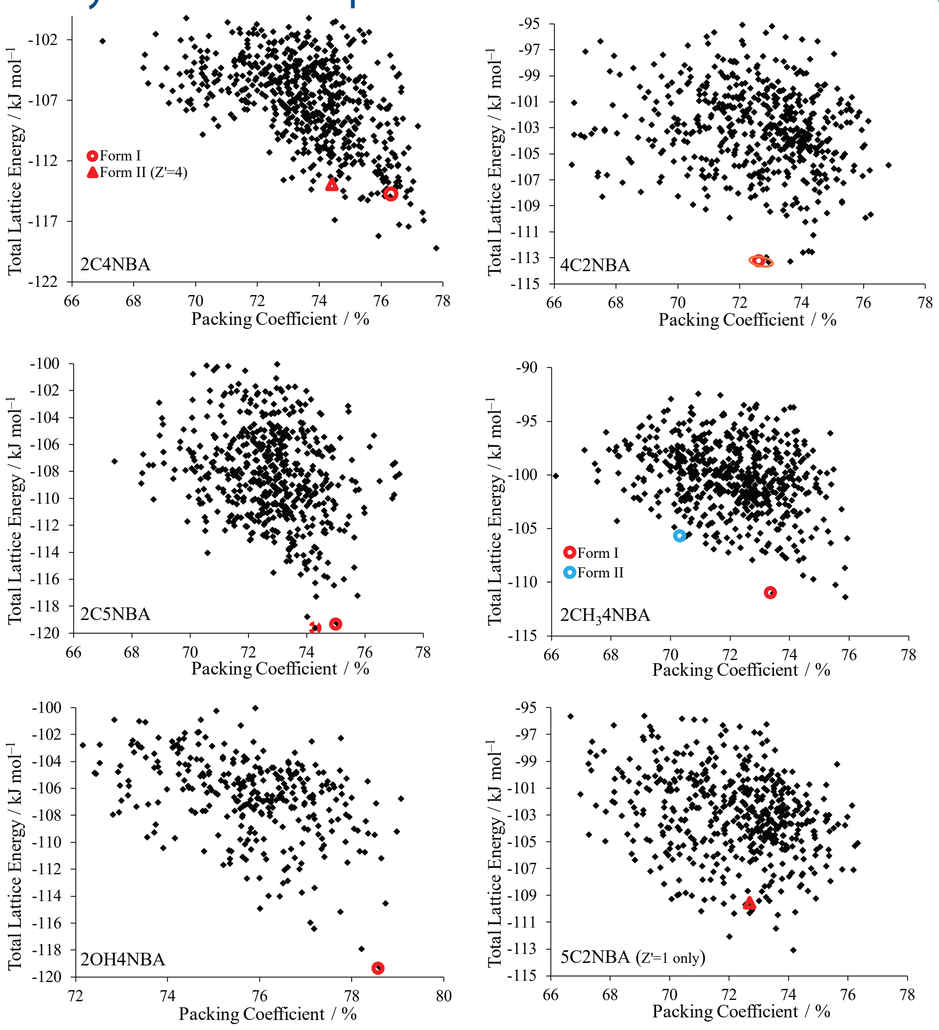
Solid form diversity





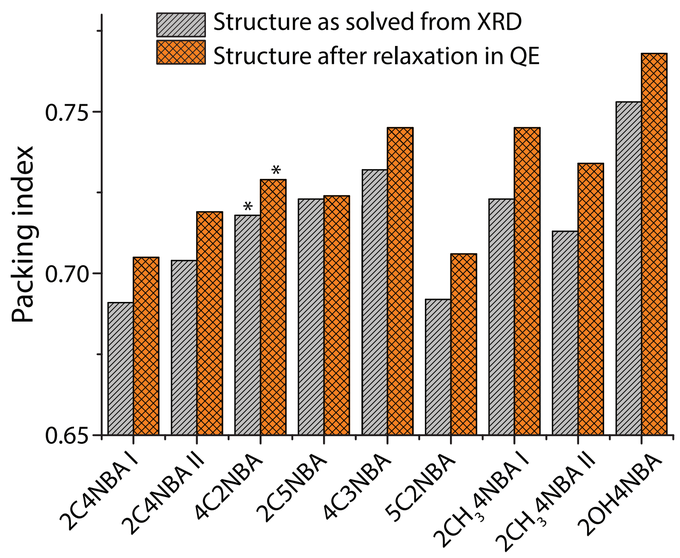
- Only 2C4NBA and $2CH_3$4NBA formed more than 1 polymorph (2 and >4 respectively)
- 2C4NBA and $2CH_3$4NBA also formed the most solvates (9 and 8)
- The least solvates were formed by 4C3NBA (4) and 5C2NBA (3).
- All compounds formed solvates with DMA and NMP, and all except 5C2NBA with DMF and DMSO.
- The next most frequent solvate formers were 1,4-dioxane (5) and acetophenone (3).
- Thus solvates of a) aprotic polar hydrogen bond acceptors and b) solvents able to form π···π dispersion interactions were obtained
- $2CH_3$4NBA tend to form solvates with smaller solvents

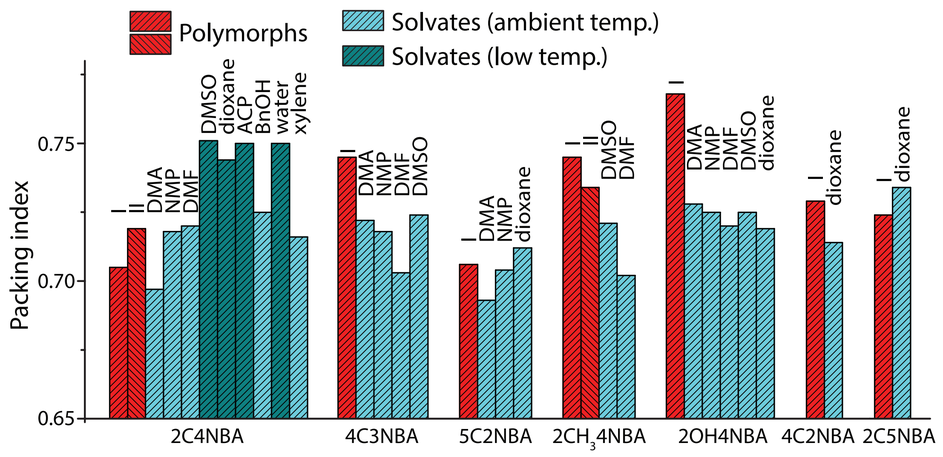
Crystal structure prediction of ansolvates



- All experimental Z′=1 structures (and Z′=2 structure for 5C4NBA) were located
- In CSP landscapes of 2C4NBA and 5C2NBA no low energy structure (ΔE_{GM} <3 kJ mol^{-1}) could be experimentally accessed.
- The packing efficiency among the predicted structures (analyzing packing coefficient and voids containing structures) are:
  $2CH_3$4NBA < 5C2NBA < 2C4NBA ≈ 4C2NBA ≈ 2C5NBA < 2OH4NBA

Packing efficiency and solve formation





- Among CNBA packing index of ansolvates correlates with the solvate formation propensity (with an exception of 5C2NBA)
- Only for 2C4NBA solvate formation is associated with the increase of the packing efficiency.
- If solvates don't improve packing, for most compounds only solvates with solvents providing stable associates in solution could be obtained

Associates in solution

Solvent	2C4NBA	4C2NBA	5C2NBA
	ΔG_{ass} / kJ mol^{-1}		
DMA	-8.32	-10.49	-5.85
DMF	-4.15	-9.95	-7.13
DMSO	-10.24	-14.18	-15.35
NMP	-7.38	-4.59	-2.61
THF	+1.15		
1,4-dioxane	+1.27		
acetophenone	+5.04		
BnOH	+5.96		
Acetone	+6.54		
IPA	+8.38		
DMC	+8.49		
toluene	+9.98		

- The most stable associates were observed for the most probbable solvate formers, thus stable associates in solution can lead to the solvate formation
- The association energy correlates with interaction energy in crystal structure
- Effect of solvent geometry is also involved in selection of stable solvates
- Other factors determine the absence of DMSO and DMF solvates of 5CNBA.

Acknowledgments

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