AN APPROACH FOR PREDICTION OF SOLID SOLUTION FORMATION POSSIBILITY OF CHEMICALLY SIMILAR MOLECULES USING CALCULATION OF LATTICE AND INTERMOLECULAR INTERACTION ENERGY

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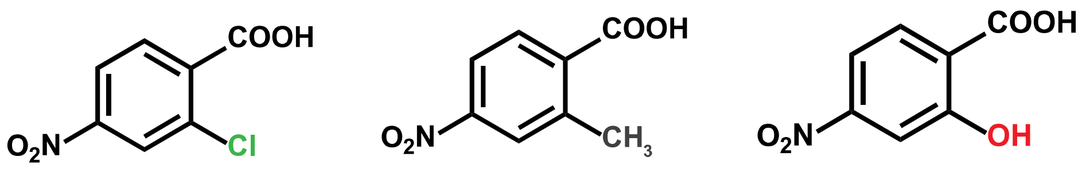
Introduction

Several 2-substituted 4-nitrobenzoic acid **(NBA)** derivatives (see below) were selected as model compounds because of their availability and chemically similar structures, in which the different group/atom **(-Cl, -CH_3 or -OH)** does not significantly affect the dominant intermolecular interactions – hydrogen bonds formed by the carboxylic group.



2C4NBA 2$CH_3$4NBA 2OH4NBA

Molecular structures of studied 2-substituted 4-nitrobenzoic acid derivatives

Aims

- To perfrom crystallization experiments of binary systems of various 2-substituted 4-nitrobenzoic acid derivatives (2OH4NBA, 2$CH_3$4NBA and 2C4NBA) to experimentally determine the information about formation of solid solutions
- To identify possible factors which could be used in prediction of the formation of solid solutions between such chemically similar molecules[3]

Crystal structures of studied nitrobenzoic acid derivatives

	2C4NBA	2$CH_3$4NBA	2OH4NBA
	I	I	I
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a / Å	10.833(3)	4.9248(10)	3.8015(1)
b / Å	5.8573(14)	11.8428(2)	11.6936(4)
c / Å	13.497(3)	13.6012(2)	16.2761(5)
α / °	90	90	90
β / °	105.734(4)	92.036(2)	94.506(2)
γ / °	90	90	90
V / Å^3	824.32	792.76	721.28
$\rho_{calc.}$ / g cm^{-3}	1.624	1.518	1.687
Z, Z′	4, 1	4, 1	4, 1

The commercially available 2OH4NBA, 2C4NBA and 2CH34NBA all correspond to polymorph I of the respective compound. All of these structures correspond to monoclinic system *P21/c* space group with one independent molecules in the asymmetric unit [4]

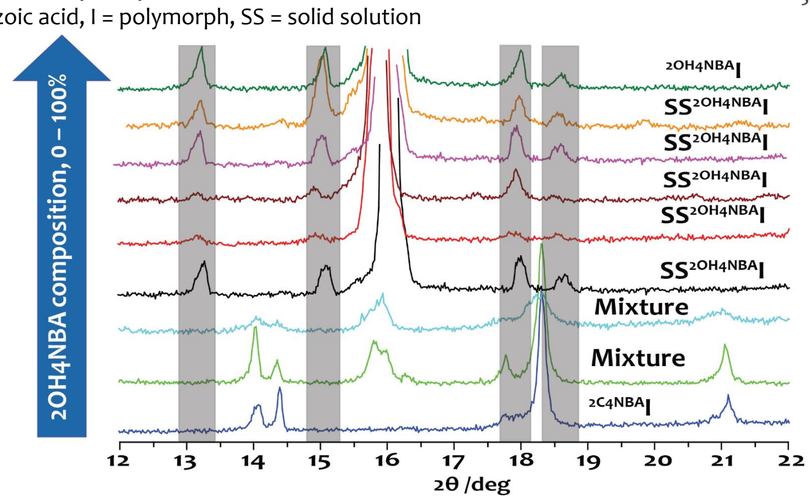
Crystallization results

The preparation of the solid solutions of **2OH4NBA$_{100-x}$2C4NBA$_x$**, **2$CH_3$4NBA$_{100-x}$2C4NBA$_x$** and **2OH4NBA$_{100-x}$2$CH_3$4NBA$_x$** was based on crystallization from solvent ethanol in different proportions (%), from 100-*x* to *x* (where $0 \le x \le 100$)[5]

Experimentally obtained crystalline phases from different nitrobenzoic acid mixtures*

Substance ratio (*x*) / %	Series of nitrobenzoic acid derivatives		
	2OH4NBA$_{100-x}$2C4NBA$_x$	**2$CH_3$4NBA$_{100-x}$2C4NBA$_x$**	**2OH4NBA$_{100-x}$2$CH_3$4NBA$_x$**
0:100	2C4NBA|	2C4NBA|	2CH34NBA|
10:90	**Mixture**	**Mixture**	SS^{2CH34NBA}|
25:75	**Mixture**	SS^{2CH34NBA}|	**Mixture**
30:70	SS^{2OH4NBA}|	SS^{2CH34NBA}|	**Mixture**
50:50	SS^{2OH4NBA}|	SS^{2CH34NBA}|	**Mixture**
70:30	SS^{2OH4NBA}|	SS^{2CH34NBA}|	SS^{2OH4NBA}|
75:25	SS^{2OH4NBA}|	SS^{2CH34NBA}|	SS^{2OH4NBA}|
90:10	SS^{2OH4NBA}|	SS^{2CH34NBA}|	SS^{2OH4NBA}|
100:0	2OH4NBA|	2CH34NBA|	2OH4NBA|

***2OH4NBA** = 2-hydroxy-4-nitrobenzoic acid, **2Cl4NBA** = 2-chloro-4-nitrobenzoic acid, **2$CH_3$4NBA** = 2-methyl-4-nitrobenzoic acid, I = polymorph, SS = solid solution



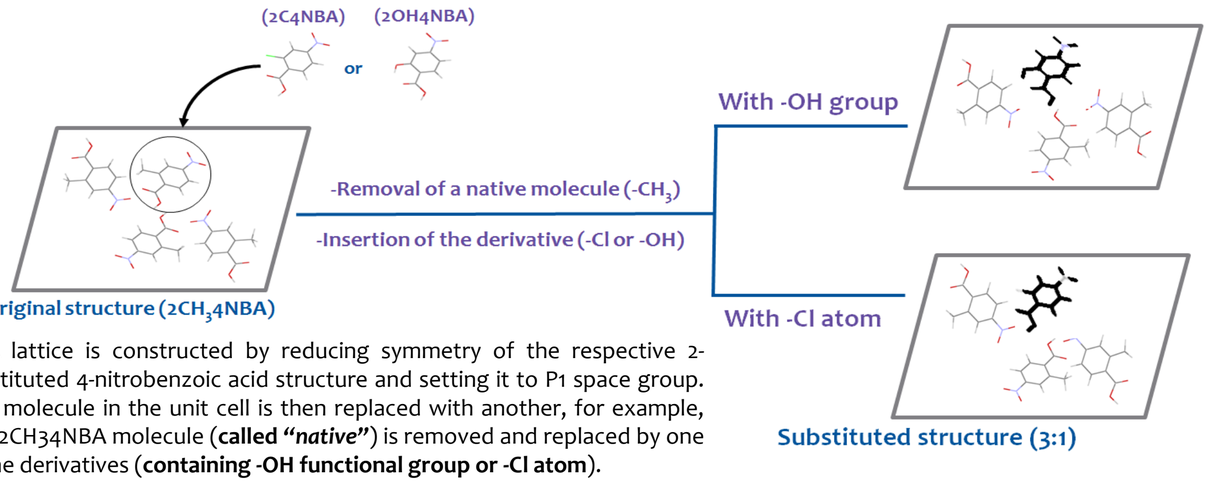
XRPD patterns for **2OH4NBA$_{100-x}$2C4NBA$_x$** mixtures after crystallization, highlighted are regions where peaks of the crystal structure of original 2OH4NBA polymorph I (upper line) will appear.

Background

Organic solids are able to form very wide range of crystalline structures of different compositions – including polymorphs, solvates, co-crystals and solid solutions. Both geometric and chemical aspects, such as molecule dimensions, symmetry, and intermolecular interactions, are important in understanding solid state properties of all these phases.[1] In last decade research of solid solutions has increased significantly and has become common in crystal engineering. While analysing solid solutions and their molecular packing, more and more attention is paid to structural aspects that promotes and are responsible for the formation of solid solutions in two-component systems.[2]

Molecular modeling

Lattice as well as intermolecular interaction energies were calculated for original, fully isostructural and substituted structure (schematic example see below).



A lattice is constructed by reducing symmetry of the respective 2-substituted 4-nitrobenzoic acid structure and setting it to P1 space group. One molecule in the unit cell is then replaced with another, for example, one 2CH34NBA molecule (**called "*native*"**) is removed and replaced by one of the derivatives (**containing -OH functional group or -Cl atom**).

Computational calculations

Lattice energies of various structures of 2-substituted 4-nitrobenzoic acid derivatives

Molecule	Replace with	$E_{lattice}$ / kJ mol^{-1}	ΔE / kJ mol^{-1}		Replace with	$E_{lattice}$ / kJ mol^{-1}	ΔE / kJ mol^{-1}	
		Original	**Subst.**	**Isostr.**		**Original**	**Subst.**	**Isostr.**
2OH4NBA	Cl	-139.8	0.9	0.9	CH_3	-139.8	1.1	1.6
2C4NBA	CH_3	-144.0	0.3	-0.5	OH	-144.0	1.7	28.5
2$CH_3$4NBA	Cl	-140.6	0.1	4.6	OH	-140.6	0.1	10.4

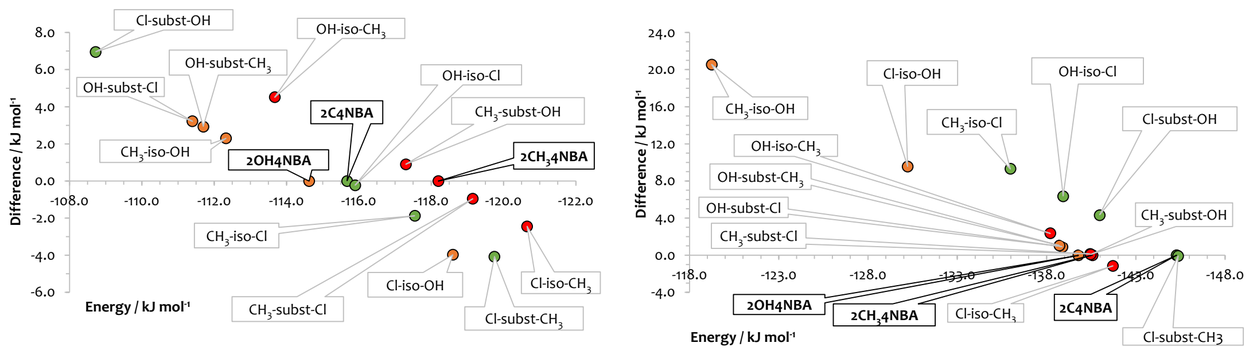
Intermolecular interaction energies of various structures of 2-substituted 4-nitrobenzoic acid derivatives

Molecule	Replace with	$E_{int.}$ / kJ mol^{-1}	ΔE / kJ mol^{-1}		Replace with	$E_{int.}$ / kJ mol^{-1}	ΔE / kJ mol^{-1}	
		Original	**Subst.**	**Isostr.**		**Original**	**Subst.**	**Isostr.**
2OH4NBA	Cl	-114.6	3.2	-4.0	CH_3	-114.6	2.9	2.3
2C4NBA	CH_3	-115.7	-4.1	-1.9	OH	-115.7	7.0	-0.2
2$CH_3$4NBA	Cl	-118.2	-0.9	-2.5	OH	-118.2	0.9	4.5

Analysis of the molecular modelling results

a) Intermolecular interaction energy

b) Lattice energy



The computed lattice and intermolecular interaction energy of the simulated structures (both isostructural and substituted) is much higher (almost in all cases) than the energy of the original structure– a positive (**ΔE > 0**) value for energy, indicating that the formation of a solid solution is not expected. On the other hand, if it is lower than the energy of the original sturcuture (**ΔE < 0**), it is likely that the two compounds will crystallize separately and will form solid solutions with each other in the given combination. Finally, if it is close to zero (**ΔE ≈ 0**), replacement is not introducing notable energy change and solid solution formation also might be expecte[6]

Conclusions

- A good prediction of the different experimental phase behaviors observed for these systems has been achieved meaning that the computational studies could be used to predict the solid solution formation for binary systems of various 2-substituted 4-nitrobenzoic acid derivatives. The results show that the lattice energy could be used to determine if the respective solid solution will form, but do not allow prediction of solid solution formation having specific maximum ratios.
- Having been successful with these model molecules, research will proceed with molecules that are more complex in order to understand possible factors, both geometric and energetic, which could systematize factors responsible for the formation of solid solutions.

Notes and references

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