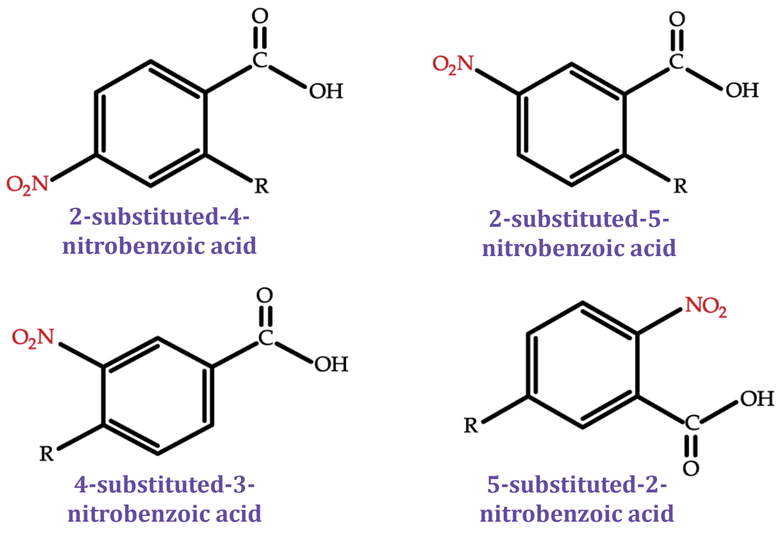
COMPUTATIONAL PREDICTION AND EXPERIMENTAL CONFIRMATION OF SOLID SOLUTION FORMATION FROM DIFFERENT NITROBENZOIC ACID DERIVATIVES AND THEIR ISOMERS

Kristaps Saršūns*, Agris Bērziņš
Faculty of Chemistry, University of Latvia, Riga, Latvia; kristaps.sarsuns@lu.lv

LATVIJAS UNIVERSITĀTE
UNIVERSITY OF LATVIA
Laboratory of Molecular Crystals

Introduction

Several nitrobenzoic acid (**NBA**) derivatives ***(-chloro, -methyl, -hydroxyl)*** and their isomers (see below), such as 2-substituted 4-nitrobenzoic acid (**24NBA**), 2-substituted 5-nitrobenzoic acid (**25NBA**), 4-substituted 3-nitrobenzoic acid (**43NBA**) and 5-substituted 2-nitrobenzoic acid (**52NBA**), were selected as model compounds because of their availability and chemically similar structures[1].



R = chlorine atom (-Cl), hydroxyl group (-OH) or methyl group (-CH_3)

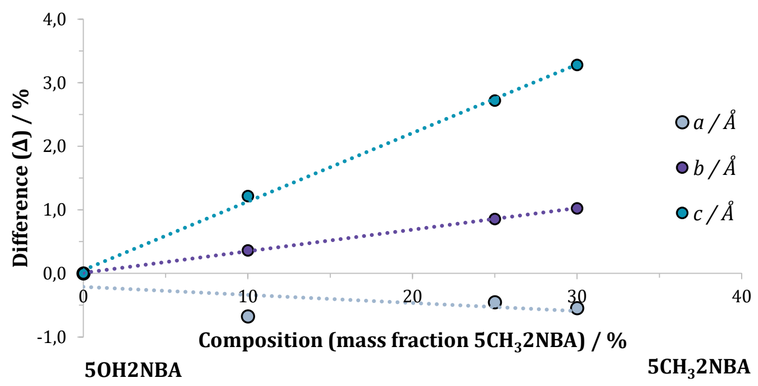
Molecular structures of various nitrobenzoic acid derivatives and their isomers

All corresponding to polymorph I of the respective compound were used as received.

Aims

- To perfrom crystallization experiments between binary systems of various substituted nitrobenzoic acid derivatives ant their isomers 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 **(SS)** between chemically similar molecules.

Structural aspects of nitrobenzoic acid solid solutions



*Crystalline lattice parameters (**a**, **b** and **c**) changes depending on the content of **5CH$_3$2NBA in 5CH$_3$2NBA$_{100-x}$5OH2NBA$_x$** solid solutions.*

In the case of non-solvated solid solutions, it can be observed that the crystal lattice parameters, depending on the content of substituted nitrobenzoic acid derivative, form a monotonous function, this means that the ***Vegard's Law*** is fulfilled[4].

Abstract

Crystallization experiments of mixtures of various substituted nitrobenzoic acid derivatives and their isomers, were used to determine the experimental information about that the solid solutions can form between those substances. Crystalline phases that were obtained during the work, were characterized by combination of use of X-ray powder diffraction (**XRPD**) and thermal analysis (**DSC/TG**), also using the nuclear magnetic resonance spectroscopy (**^{1}H-NMR**), information about stoichiometric ratios, of mixtures of different nitrobenzoic acid derivatives and their isomers in crystallization products, were obtained[2].

Furthermore, using quantum chemical calculations for information about structural and energetic aspects were carried out to identify possible factors, which could be used in prediction of the formation of solid solutions in binary systems of chemically similar molecules[3].

Quantum chemical calculations

Information about crystal lattice energy changes for different nitrobenzoic acid derivatives and their isomers*

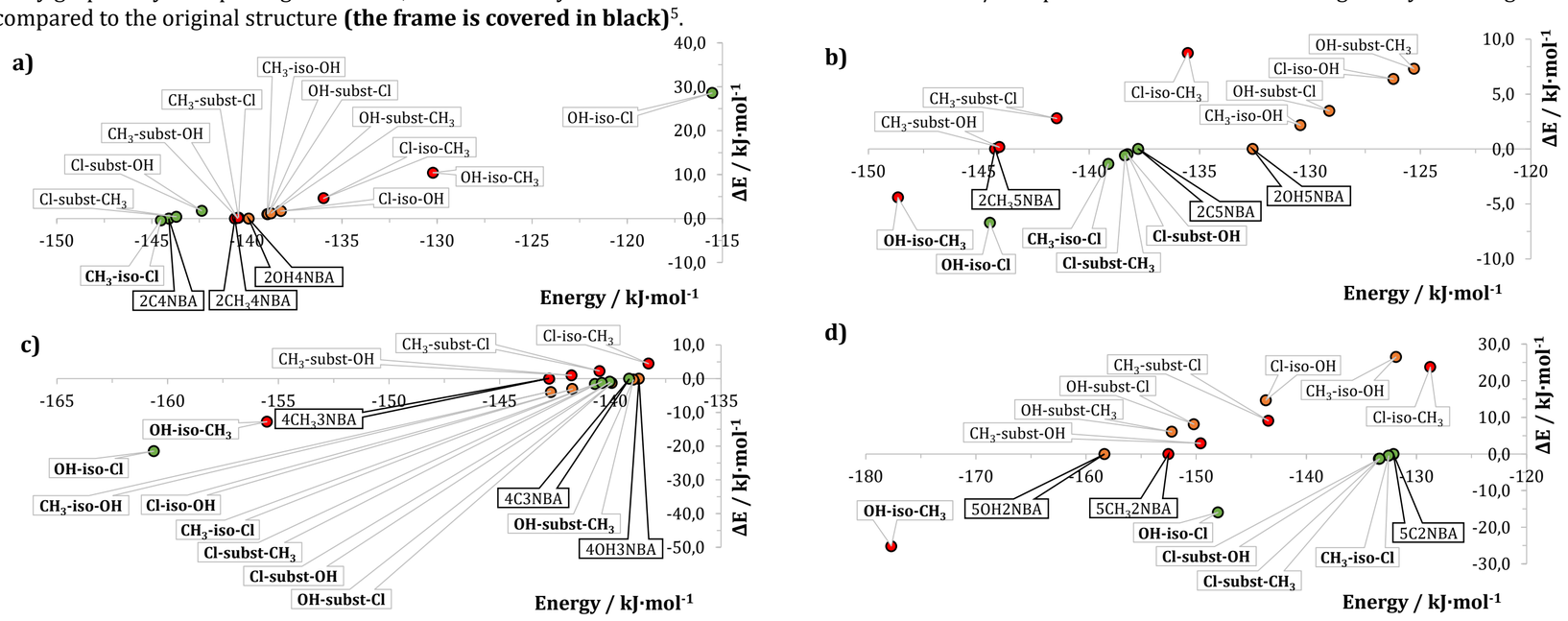
Structure	Replacement	ΔE / kJ·mol^{-1}			
		2OH4NBA	2OH5NBA	4OH3NBA	5OH2NBA
Original	-	0,0	0,0	0,0	0,0
Isostructural	Cl-iso-OH	1,0	2,2	**-4,0**	26,5
	CH_3-iso-OH	1,7	6,4	**-3,0**	14,7
Substituted	OH-subst-Cl	1,0	3,5	**-1,2**	8,1
	OH-subst-CH_3	1,2	7,3	**-0,2**	6,1
Structure	Replacement	ΔE / kJ·mol^{-1}			
		2C4NBA	2C5NBA	4C3NBA	5C2NBA
Original	-	0,0	0,0	0,0	0,0
Isostructural	OH-iso-Cl	28,6	**-6,7**	**-21,5**	**-16,0**
	CH_3-iso-Cl	**-0,4**	**-1,3**	**-1,5**	**-0,4**
Substituted	Cl-subst-OH	1,7	**-0,5**	**-0,9**	**-1,3**
	Cl-subst-CH_3	0,4	**-0,6**	**-1,2**	**-1,3**
Structure	Replacement	ΔE / kJ·mol^{-1}			
		2$CH_3$4NBA	2$CH_3$5NBA	4$CH_3$3NBA	5$CH_3$2NBA
Original	-	0,0	0,0	0,0	0,0
Isostructural	Cl-iso-CH_3	4,7	8,7	4,5	23,8
	OH-iso-CH_3	10,4	**-4,4**	**-12,8**	**-25,2**
Substituted	CH_3-subst-Cl	0,2	2,8	2,3	9,1
	CH_3-subst-OH	0,2	0,2	1,0	2,9

(calculated according to *VC-relax* and *SCF* solution)

* - **ΔE < 0 (colored in bold)**, it is likely that the two compounds will crystallize separately and will form solid solutions with each other in the given combination[6].

Energetic aspects of nitrobenzoic acid solid solutions

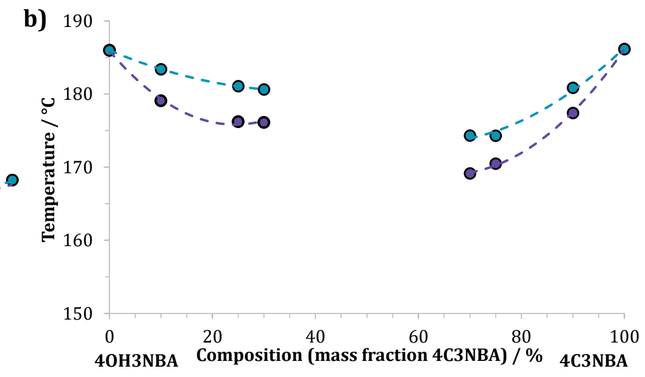
By graphically interpreting the results, it can be clearly seen in which cases the isostructural and/or replaced structure is more energetically advantageous compared to the original structure **(the frame is covered in black)**[5].

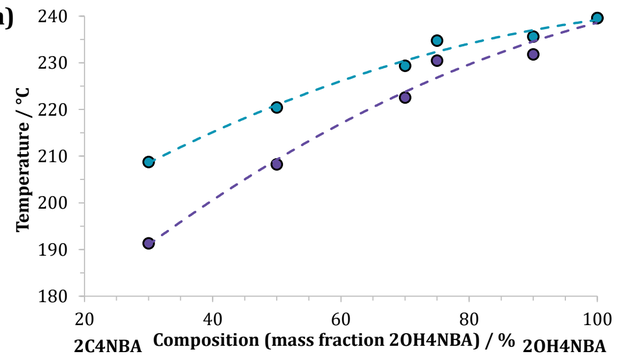


*Energy change (**ΔE**) depending on the crystal lattice energy of **a) 2-substituted 4-nitrobenzoic acid**, **b) 2-substituted 5-nitrobenzoic acid**, **c) 4-substituted 3-nitrobenzoic acid** and **d) 5-substituted 2-nitrobenzoic acid** (colors are marked by substitution of* group/atom (**R**): ***green** – chlorine atom, **orange** – hydroxyl group, **red** – methyl group).*

Identification of nitrobenzoic acid solid solutions

Solid solution formation can be confirmed by means of melting phase diagram. It precisely demonstrate that the various substituted nitrobenzoic acid derivatives and their isomers form solid solutions between each other, for example, when solid solution forms in the whole range of substance ratios **(a)** and at both sides - limited substance ratios **(b)**[7].





*Melting points (DSC **onset temperatures**) and maximum points (DSC **peak temperatures**) vs. mass fraction of **a) 2OH4NBA in 2OH4NBA$_{100-x}$2C4NBA$_x$** and **b) 4C3NBA in 4C3NBA$_{100-x}$4OH3NBA$_x$** solid solutions.*

Graphically depicting the **melting** of the crystallization products (*onset temperature*) depending on the weight fraction of the substituted nitrobenzoic acid derivative, as well as including the **maximum** temperature (*peak temperature*) a two-component phase diagram is formed (**$T_{melt.}$** – **solidus** and **$T_{max.}$** – **liquidus**).

Crystallization results

The preparation of the solid solutions of various nitrobenzoic acid derivatives and their isomers was based on crystallization from solvent (in this case from ethanol), in different proportions **(%)**, from ***100-x*** to ***x***, where **$0 \le x \le 100$**.

Experimentally obtained crystalline phases from different nitrobenzoic acid mixtures

System	Series of NBA derivatives	Substance ratio / %								
		0:100	10:90	25:75	30:70	50:50	70:30	75:25	90:10	100:0
2-substituted 4-nitrobenzoic acid	2OH4NBA$_{100-x}$ 2C4NBA$_x$									
	2$CH_3$4NBA$_{100-x}$ 2C4NBA$_x$									
	2OH4NBA$_{100-x}$ 2$CH_3$4NBA$_x$									
2-substituted 5-nitrobenzoic acid	2C5NBA$_{100-x}$ 2OH5NBA$_x$									
	2$CH_3$5NBA$_{100-x}$ 2C5NBA$_x$									
	2OH5NBA$_{100-x}$ 2$CH_3$5NBA$_x$									
4-substituted 3-nitrobenzoic acid	4OH3NBA$_{100-x}$ 4C3NBA$_x$									
	4$CH_3$3NBA$_{100-x}$ 4C3NBA$_x$									
	4$CH_3$3NBA$_{100-x}$ 4OH3NBA$_x$									
5-substituted 2-nitrobenzoic acid	5C2NBA$_{100-x}$ 5OH2NBA$_x$									
	5$CH_3$2NBA$_{100-x}$ 5C2NBA$_x$									
	5$CH_3$2NBA$_{100-x}$ 5OH2NBA$_x$									

Solid solution (SS) Mixture Pure phase (polymorph I)

Conclusions

- The possibility of solid solution formation in a system which contains different substituted nitrobenzoic acid derivatives and their isomers was investigated using a simple molecular modeling procedure which consists of **(I)** replacement of a given amount of *B* molecules into the *A* structure by preparing a virtual solid solution **(subst)** as well as a fully replaced isostructural phase **(iso)**; **(II)** computation of the lattice energies and intermolecular interaction energies, and comparison energy of these structures with the energy of the original structure (calculated for pure phases).
- A prediction of different experimental phase behaviors observed in these systems was achieved. Computational studies can be used to predict the formation of solid solution in binary systems of various substituted nitrobenzoic acid derivatives and their isomers. The results show that the lattice and intermolecular interaction energy can be used to determine whether the respective solid solution will form, but do not allow prediction of specific maximum ratios of formed solid solutions;
- As this modelling approach was successful, research will proceed with molecules that are more complex (for example, active pharmaceutical ingredients) in order to understand possible factors, both geometric and energetic, and systematize the factors responsible for the formation of solid solutions.

References

1. Bērziņš. A., Kons. A., Saršūns. K., Belyakov, S., Actiņš, A. *Crystal Growth & Design*, **2020**, *20(9)*, 5767-5784.
2. Lusi, M. *Cryst. Growth Des.*, **2018**, *18 (6)*, 3704-3712.
3. Fonseca, J. de C., Tenorio Clavijo, J. C., Alvarez, N., Ellena, J., Ayala, A. P. *Crystal Growth & Design*, **2018**, *18(6)*, 3441-3448.
4. Denton, A. R., Ashcroft, N. W. *Phys. Rev. A.*, **1991**, *43*, 3161-3164.
5. Thomas, S. P., Spackman, M. A. *Australian Journal of Chemistry*, **2018**, *71(4)*, 279-284.
6. Thomas, S. P., Spackman, P. R., Jayatilaka, D., Spackman, M. A. *Journal of Chemical Theory and Computation*, **2018**, *14(3)*, 1614-1623.
7. Romasanta, A. K. S., Braga, D., Duarte, M. T., Grepioni, F. *CrystEngComm.*, **2017**, *19(4)*, 653-660.

Acknowledgments

This work 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 and University of Latvia foundation trough "Mikrotīkls" doctoral scholarship in the field of exact and medical sciences.

FLPP FUNDAMENTAL AND APPLIED RESEARCH PROJECTS
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Presented at: The 2nd International Online Conference on Crystals, Online, November 10-20, 2020