EIROPAS SOCIĀLAIS FONDS

EIROPAS SAVIENĪBA

LATVIJAS UNIVERSITĀTE
ANNO 1919

IEGULDĪJUMS TAVĀ NĀKOTNĒ

DESOLVATION OF DROPERIDOL ISOSTRUCTURAL SOLVATES

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Background

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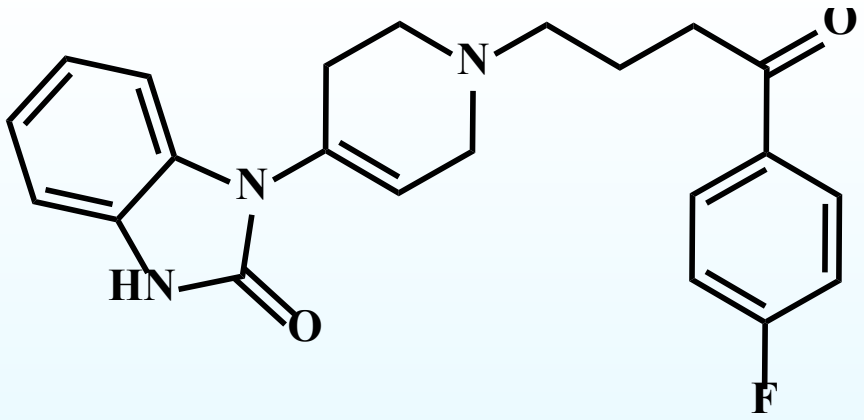
Introduction

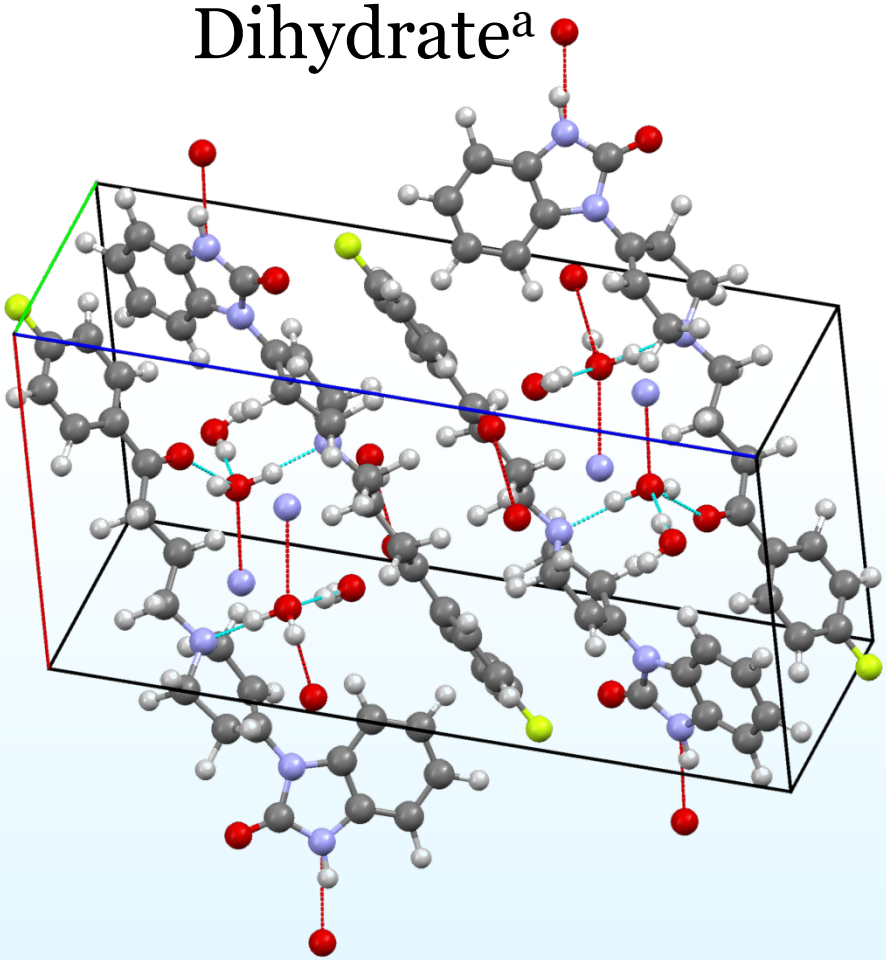
- Droperidol is known to exist in:
  - Two polymorphic forms Y and Z [a,b]
  - Dihydrate [c]
  - Nonstoichiometric hydrate [a,b]
  - Ethanol solvate [d]



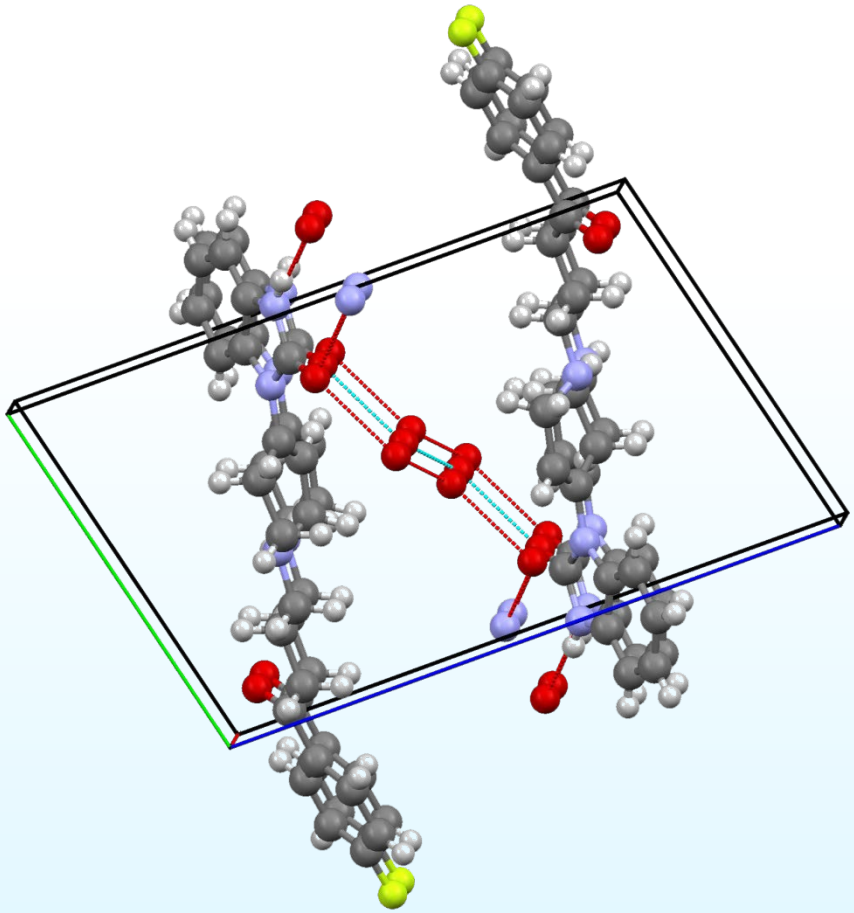
a) M. Azibi, M. Draguet-Brughmans, R. Bouche, Pharmaceutica Acta Helvetiae, 57 (1982) 182-188.
b) A. Actins, R. Arajs, S. Belakovs, L. Orola, M. Veidis, Journal of Chemical Crystallography, 38 (2008) 169-174.
c) N.M. Blaton, O.M. Peeters, C.J. De Ranter, Acta Crystallographica Section B, 36 (1980) 2828-2830.
d) C.L. Klein, J. Welch, L.C. Southall, Acta Crystallographica Section C, 45 (1989) 650-653.

Droperidol hydrates

Dihydrate[a]



Hemihydrate[b,c]



a) N.M. Blaton, O.M. Peeters, C.J. De Ranter, Acta Crystallographica Section B, 36 (1980) 2828-2830.
b) A. Actins, R. Arajs, S. Belakovs, L. Orola, M. Veidis, Journal of Chemical Crystallography, 38 (2008) 169-174.
c) L. Orola. Synthesis, structure and properties of crystalline forms of some active pharmaceutical ingredients. PhD Thesis, Riga Technical University, (2010) 170 p.

Droperidol hydrates - conclusions

- Droperidol dihydrate
  - typical stoichiometric hydrate
  - complicated dehydration process
- Droperidol hemihydrate
  - typical nonstoichiometric hydrate
  - Dehydration gives isomorphic dehydrate

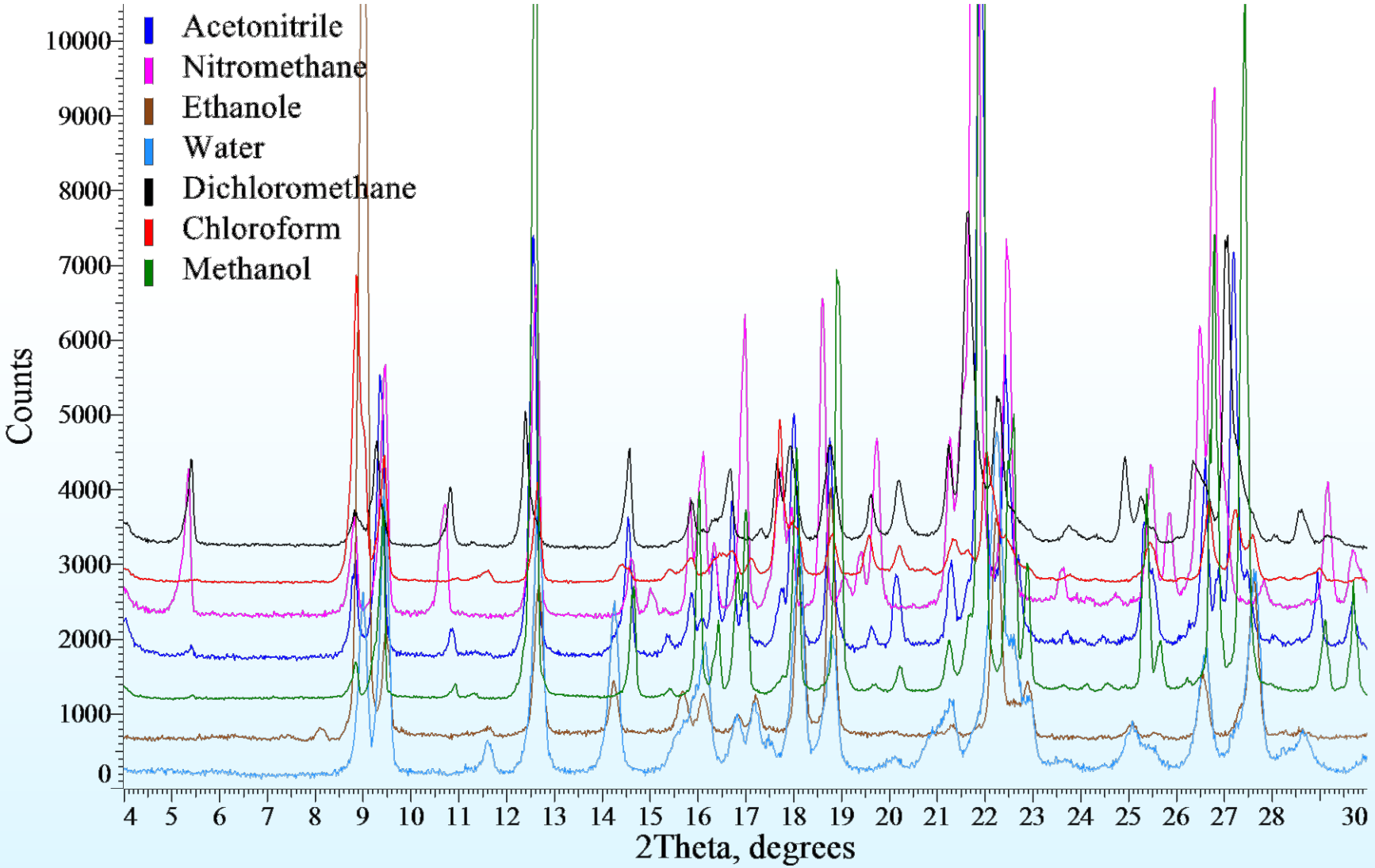
Outline

- **Preparation and characterization of solvates**
  - Crystallization
  - Characterization
  - Crystal structure determination
- Droperidol ethanol and methanol solvates
  - Sorption-desorption isotherms
  - Systematic lattice parameter changes
- Desolvation kinetics
  - Desolvation by controlling PXRD pattern
  - Kinetic parameters from isothermal experiments
  - Solvent exchange experiment
- Conclusions

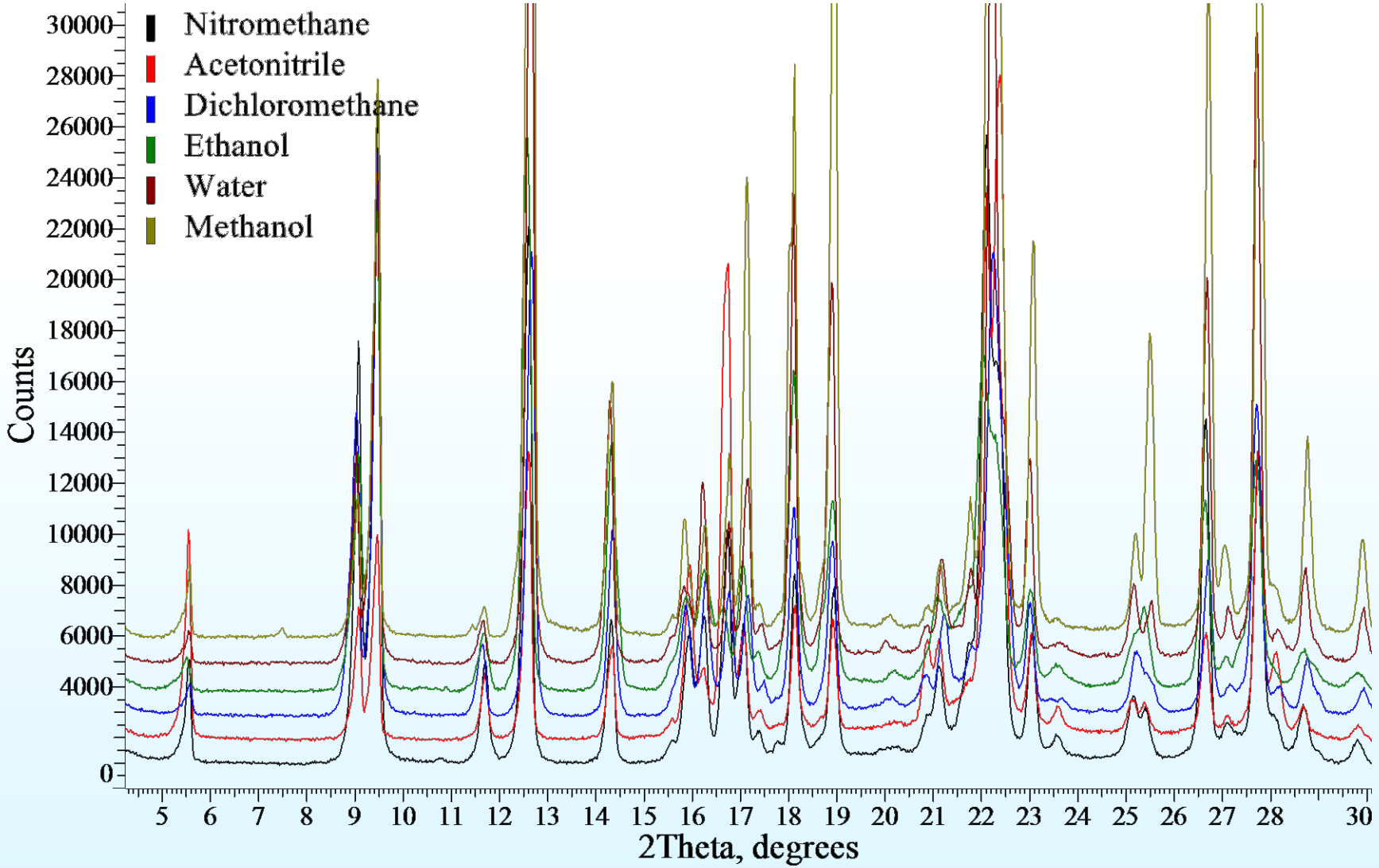
Crystallization of droperidol

	Solvent	Phase	Solvent	Phase
Aprotic polar	acetone	Z	1,4-dioxane	-
	acetonitrile	Solvate	ethylacetate	Z
	n-buthylacetate	Z	nitromethane	Solvate
	cyclohexanon	-	3-pentanone	Z
	dichloromethane	Solvate		
Hydrogen bond donors	Acetic acid	Solvate	Methanol	Solvate
	1-butanol	Z	1-pentanol	-
	Carbon tetrachloride	Z	1-propanol	Z
	Chloroform	Solvate	2-propanol	Z
	Cyclohexanol	-	Water	DH/NSTH
	Ethanol	Solvate		
Electron pair donors / Aromatic apolar or lightly polar				
	terc-buthylmethyl ether	Z	toluene	Z
	tetrahydrofurane	Z/Y		

PXRD patterns of solvates



Desolvation of solvates

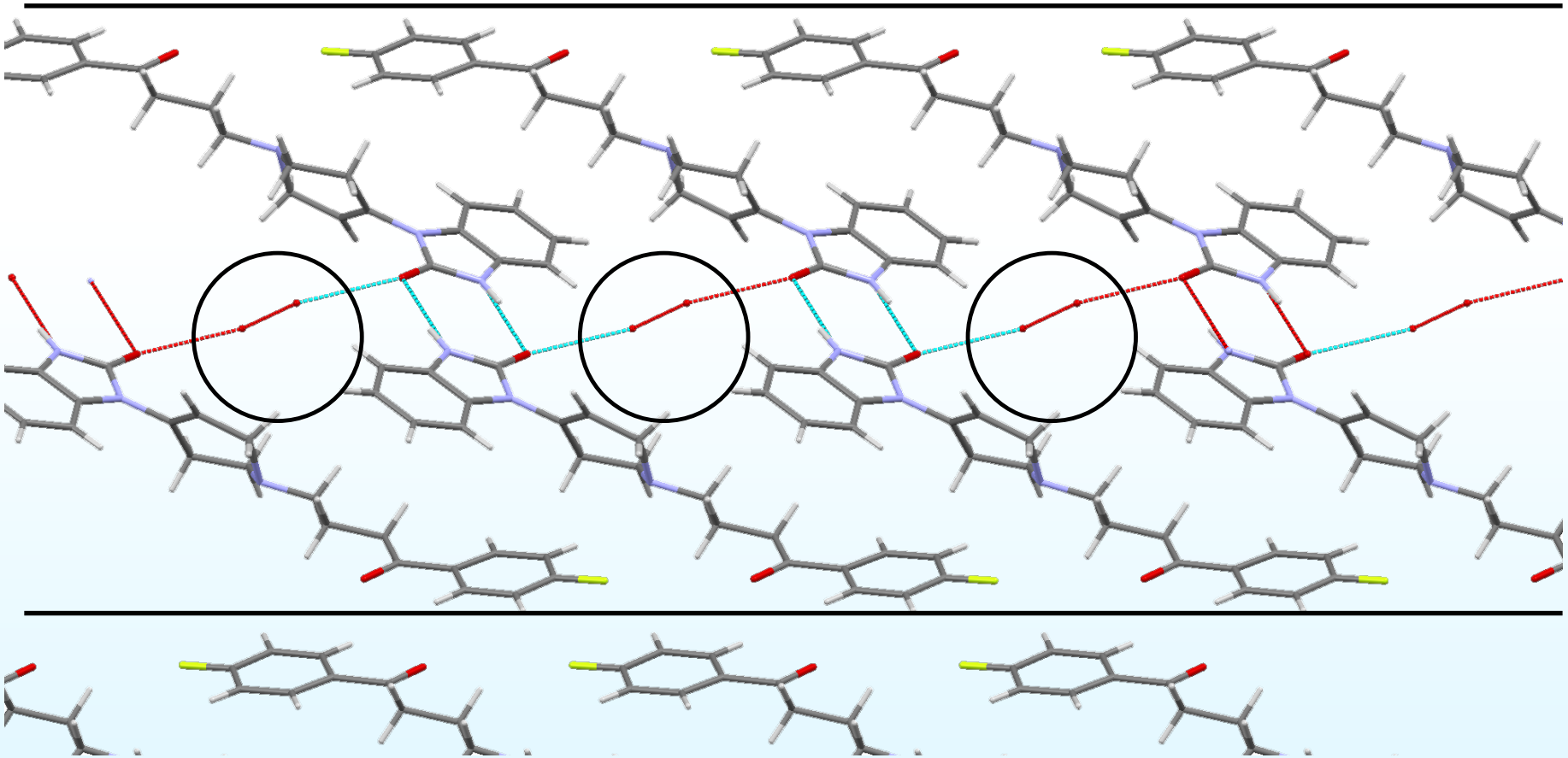


Crystal structure of solvates

Parameter	Solvent					
	Water [a]	Ethanol [b]	Methanol	Nitrometane	Acetonitrile	Ethanol
Stoichiometry	0.5	0.5	0.5	0.5	0.5	0.5
Space group	P-1	P-1	P1	P1	P1	P-1
a, Å	6.2842(15)	6.083(3)	6.0671(2)	6.06730(10)	6.0870(2)	6.08400(10)
b, Å	10.1473(8)	10.296(1)	10.2183(4)	10.1884(3)	10.2177(3)	10.2978(3)
c, Å	16.1854(2)	16.018(2)	16.2078(8)	16.4237(5)	16.2642(6)	16.1737(5)
α, °	102.554	100.93(1)	101.3130(10)	99.8303(13)	101.2051(11)	100.9299(10)
β, °	91.917(14)	92.72(2)	93.208(2)	92.2880(12)	92.7447(10)	92.6382(10)
γ, °	99.316(12)	96.27(2)	96.996(2)	95.6243(18)	96.7569(19)	95.9415(15)
V, Å^3	991.614	976.735	974.654	993.864	982.777	987.346
Z, Z`	2, 1	2, 1	2, 2	2, 2	2, 2	2, 1
T, K	293	193	193	193	193	193
R	5.09	5.81	6.18	6.42	5.55	6.80

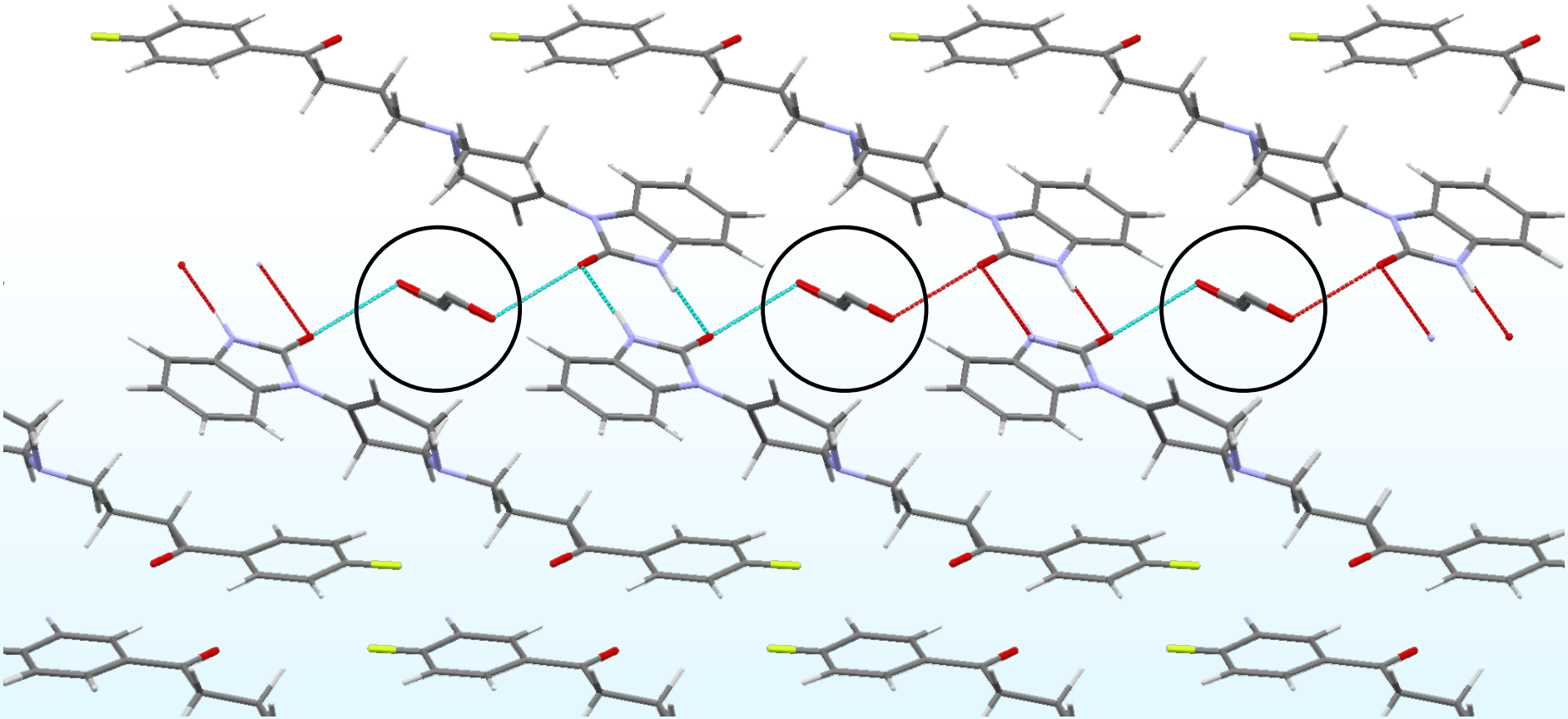
a) A. Actins, R. Arajs, S. Belakovs, L. Orola, M. Veidis, *J Chem Crystall*, 38 (2008) 169-174.
b) C.L. Klein, J. Welch, L.C. Southall, Acta Crystallographica Section C, 45 (1989) 650-653.

Crystal structure of solvates - water



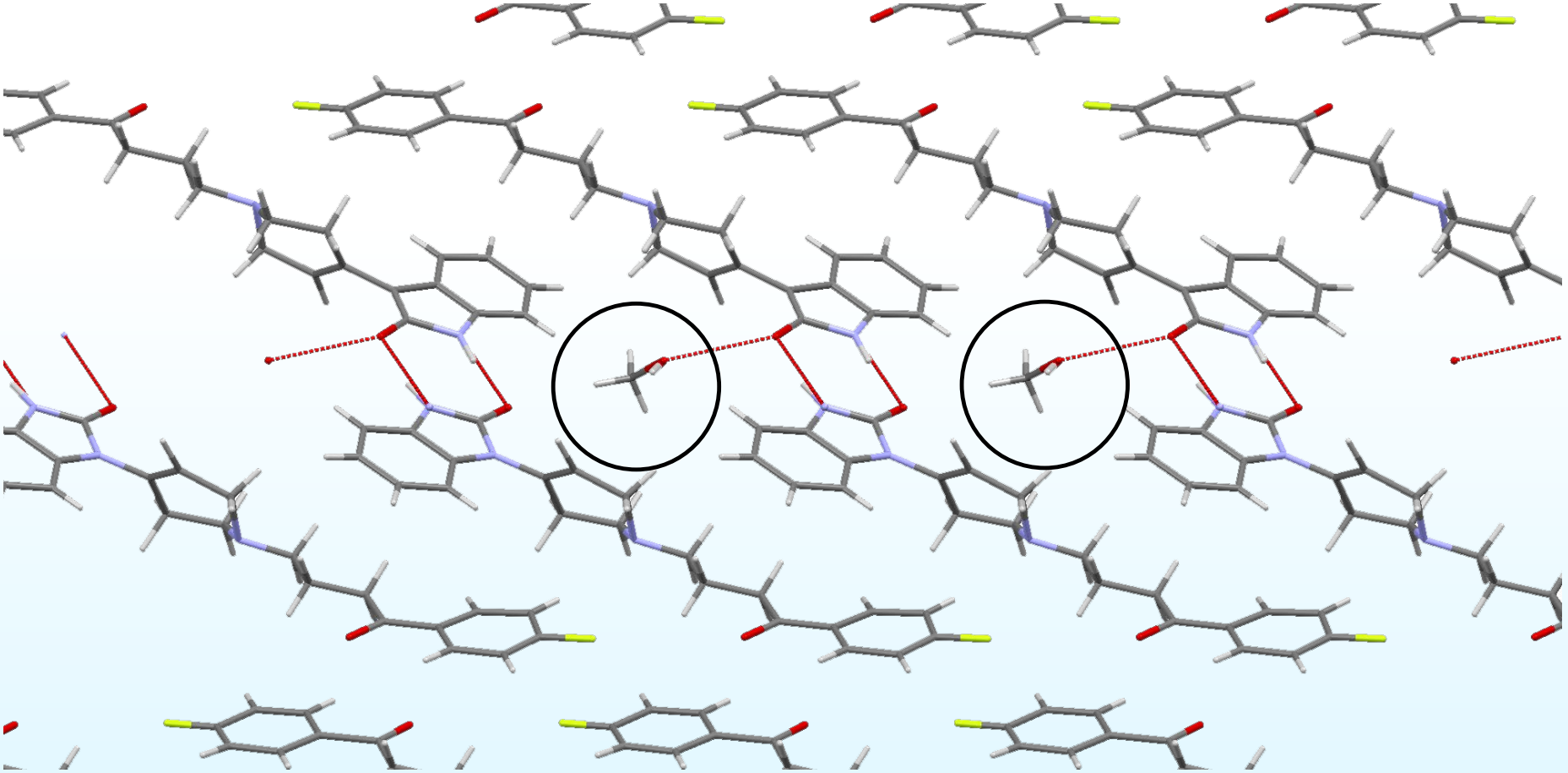
a) A. Actins, R. Arajs, S. Belakovs, L. Orola, M. Veidis, Journal of Chemical Crystallography, 38 (2008) 169-174.

Crystal structure of solvates - ethanol

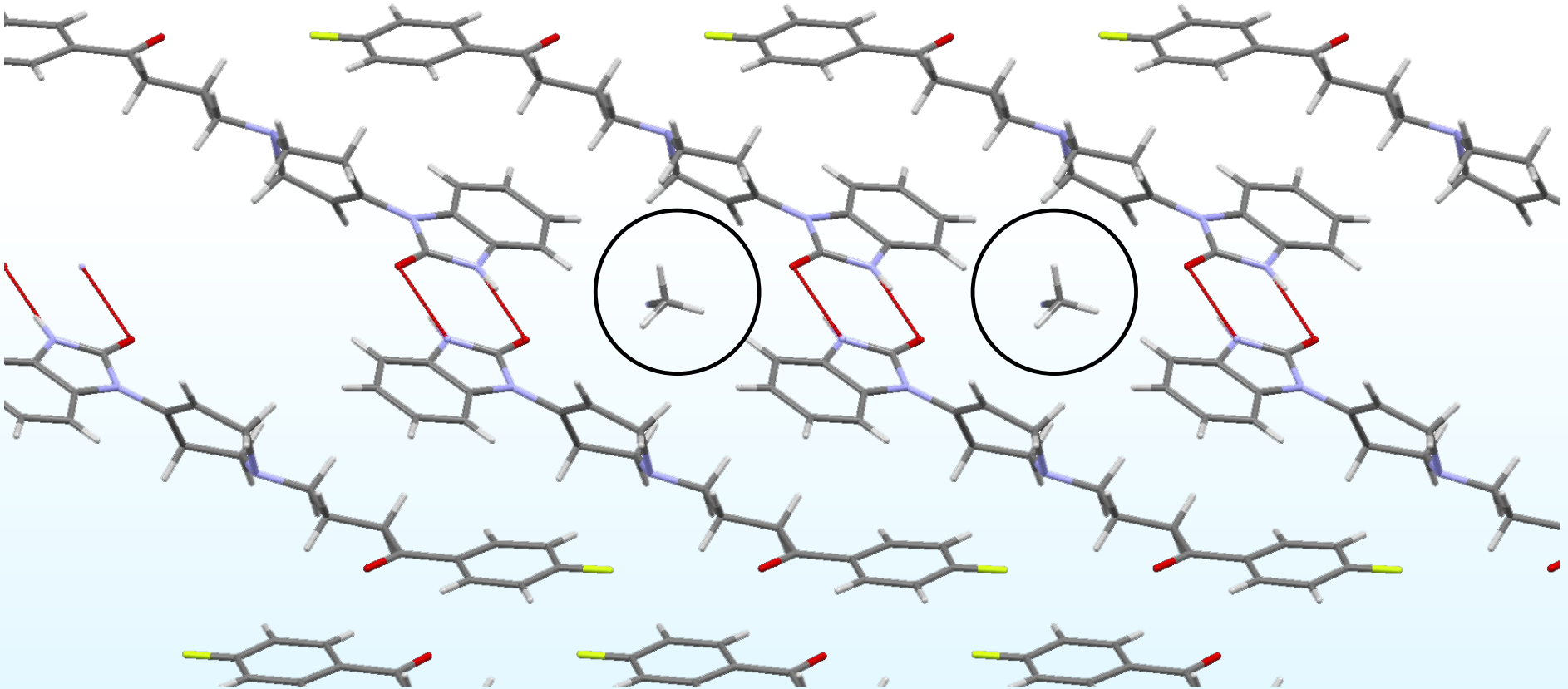


a) C.L. Klein, J. Welch, L.C. Southall, Acta Crystallographica Section C, 45 (1989) 650-653.

Crystal structure of solvates - methanol



Crystal structure of solvates - acetonitrile



Outline

- Preparation and characterization of solvates
  - Crystallization
  - Characterization
  - Crystal structure determination
- **Droperidol ethanol and methanol solvates**
  - Sorption-desorption isotherms
  - Systematic lattice parameter changes
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  - Desolvation by controlling PXRD pattern
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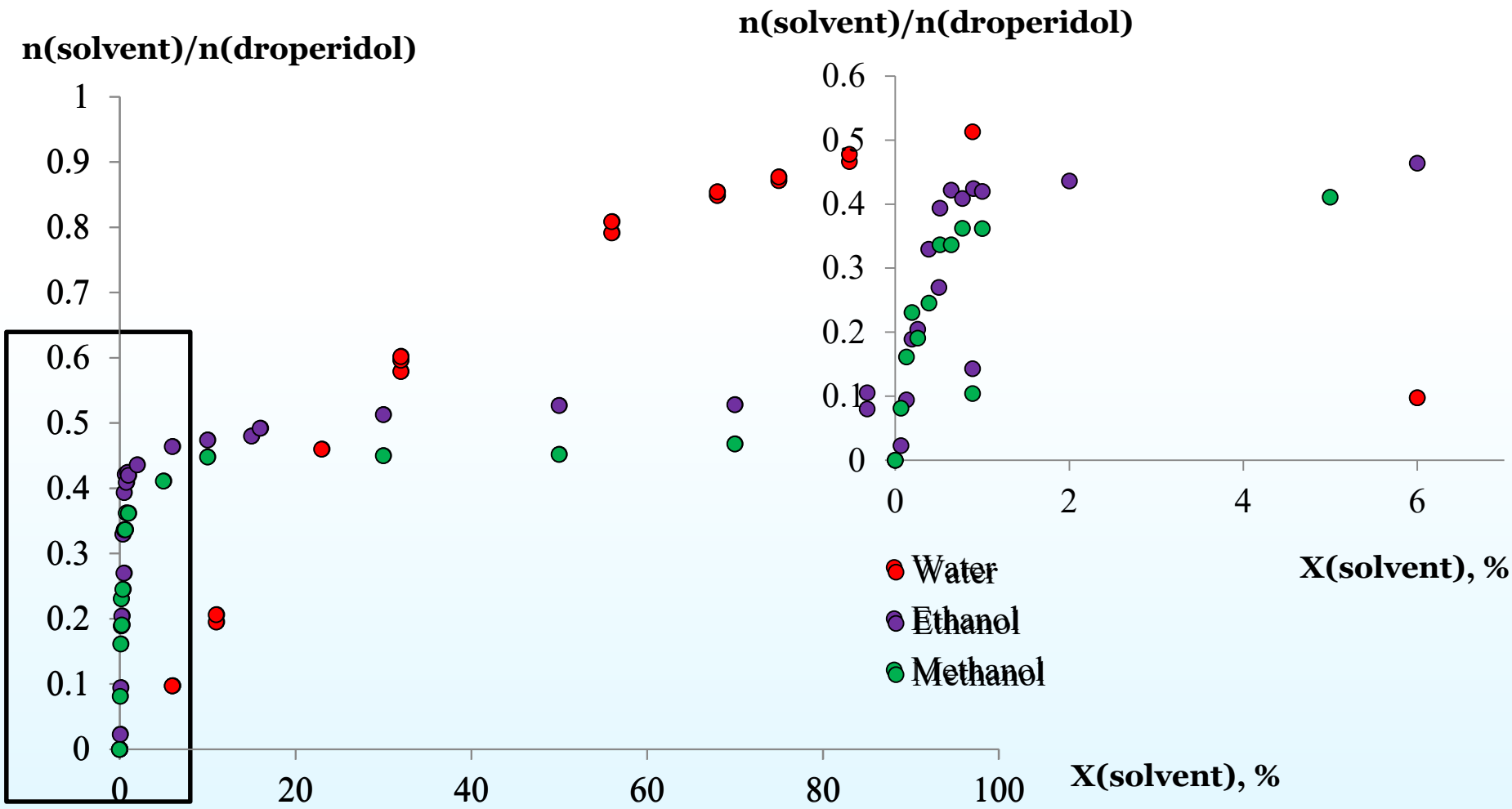
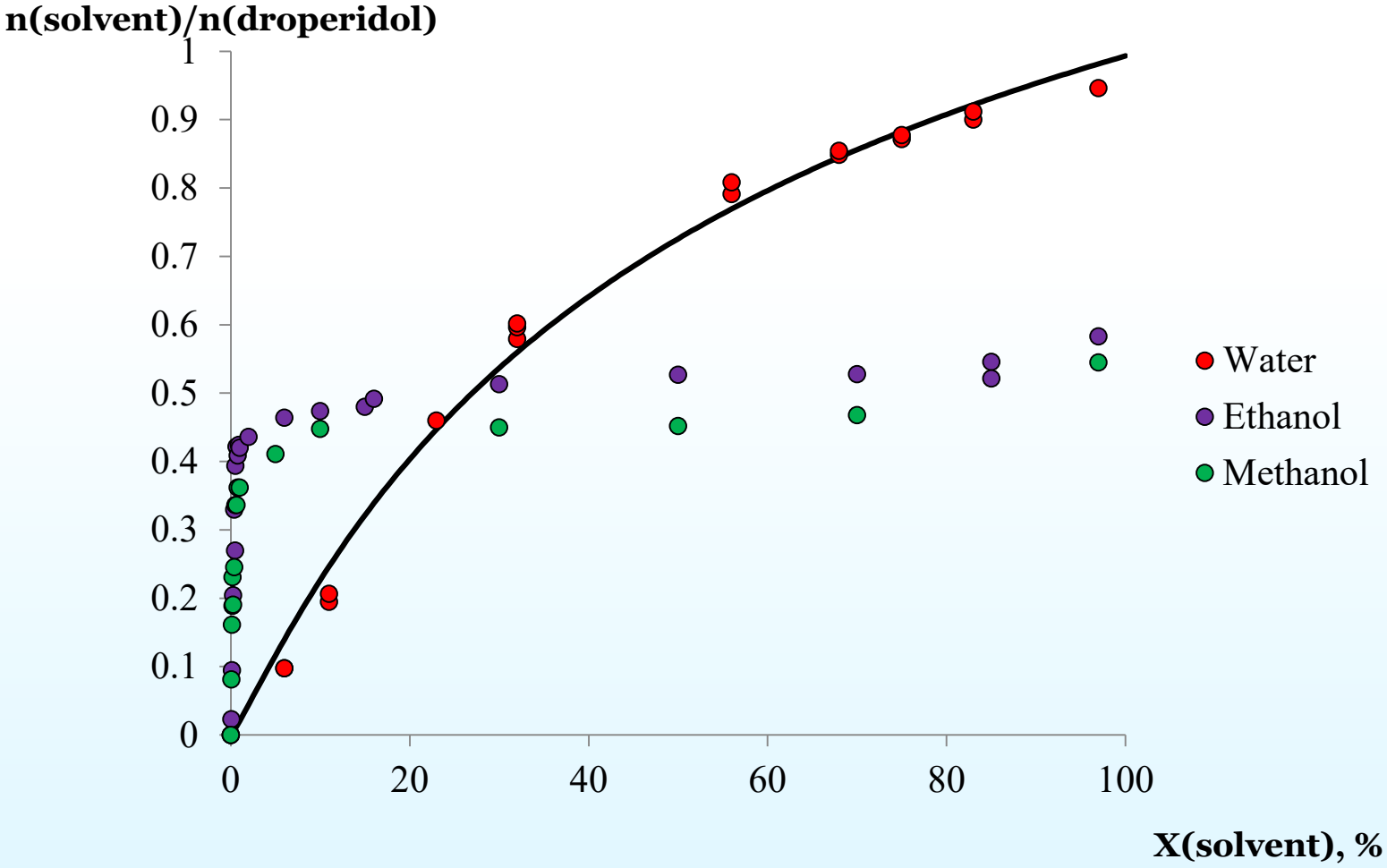
  - Solvent exchange experiment
- Conclusions

Sorption-desorption isotherms



Sorption-desorption isotherms of droperidol solvates

Sorption-desorption isotherms



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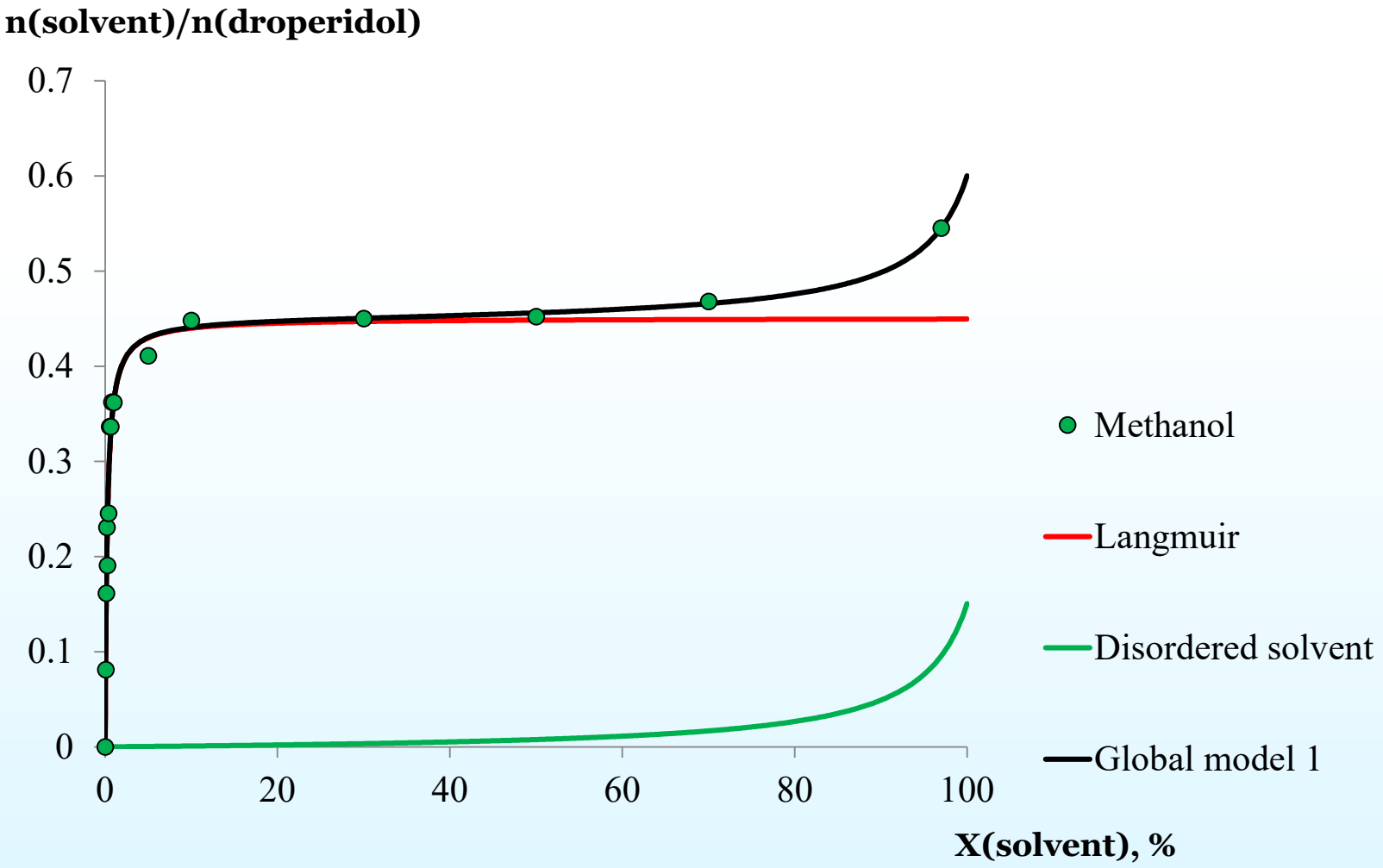
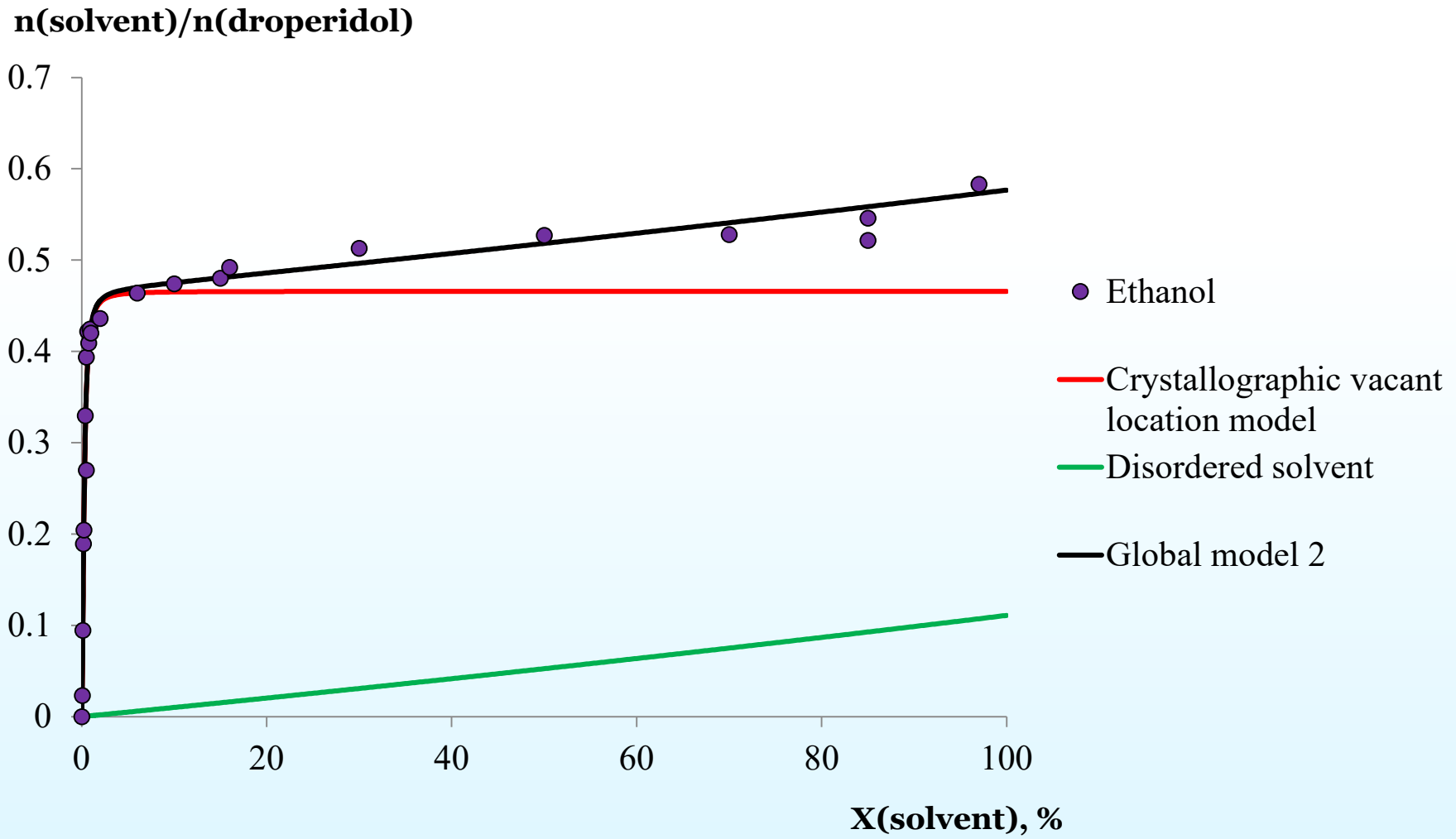
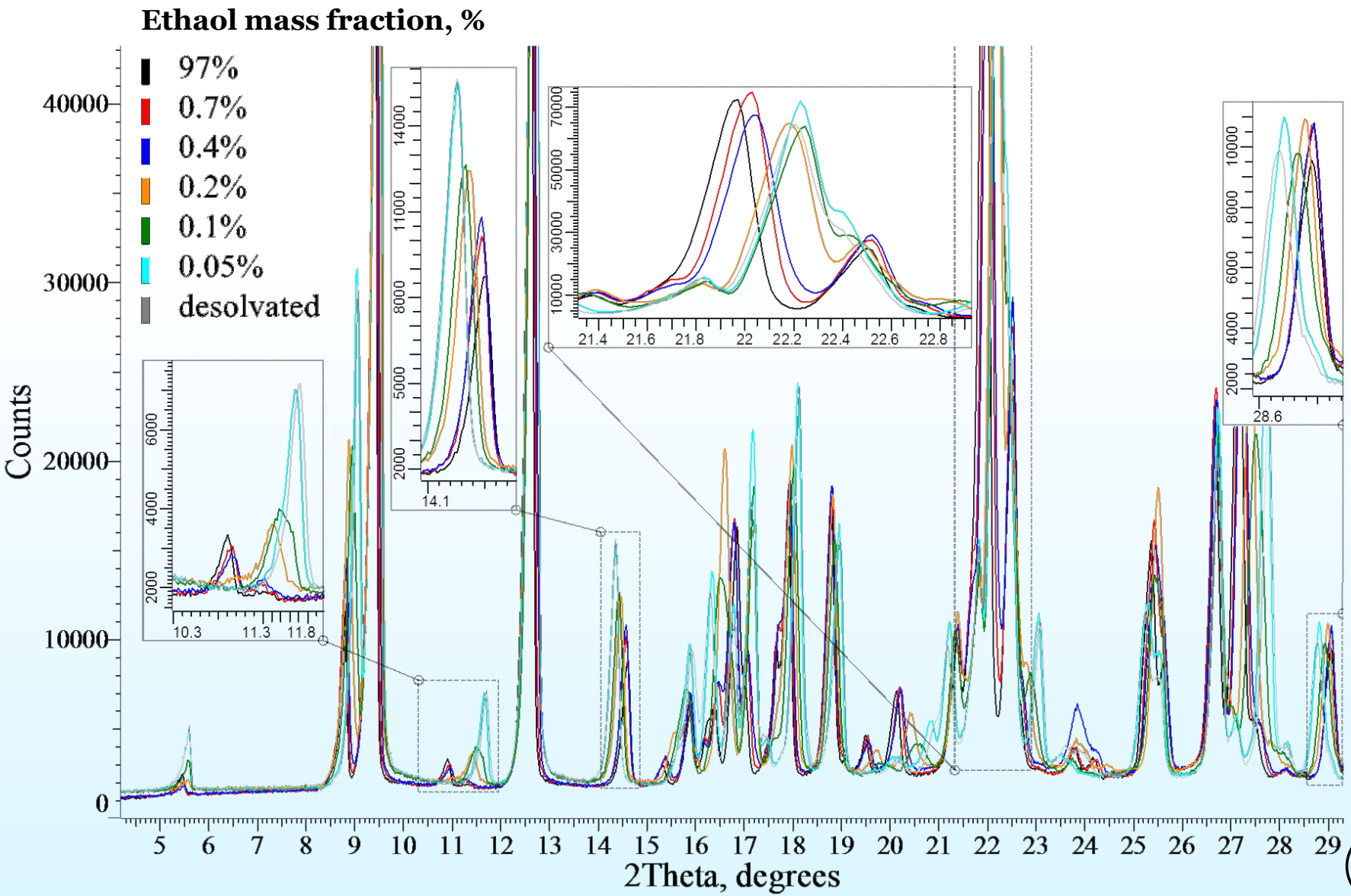


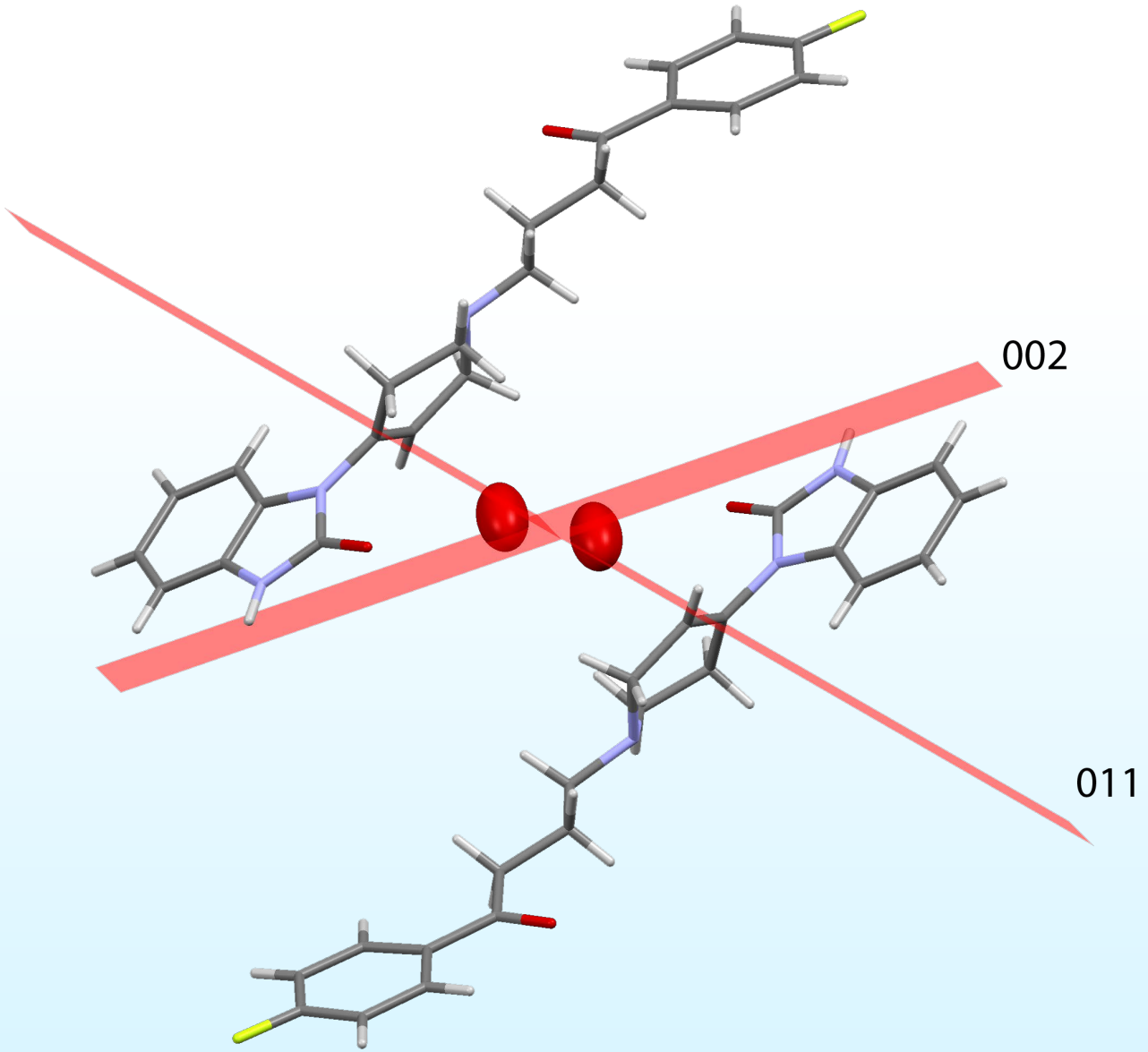
Sorption-desorption isotherms



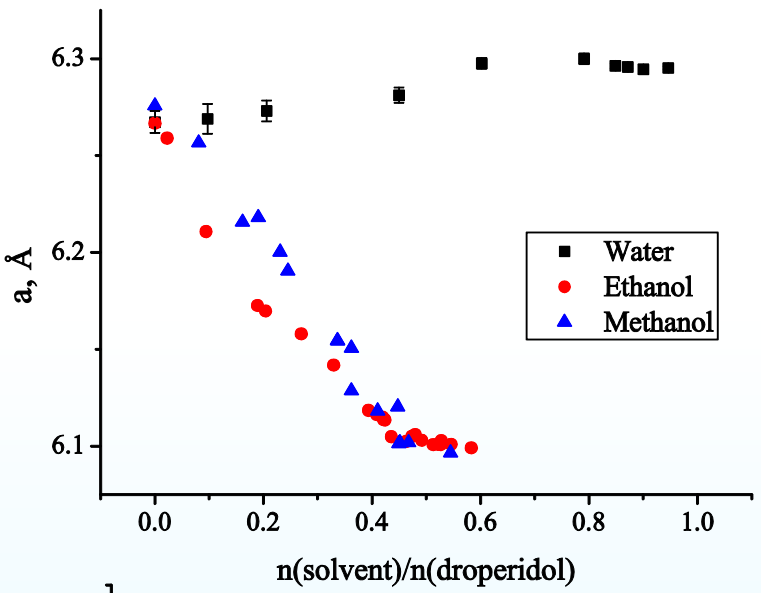
PXRD pattern changes of ethanol solvate

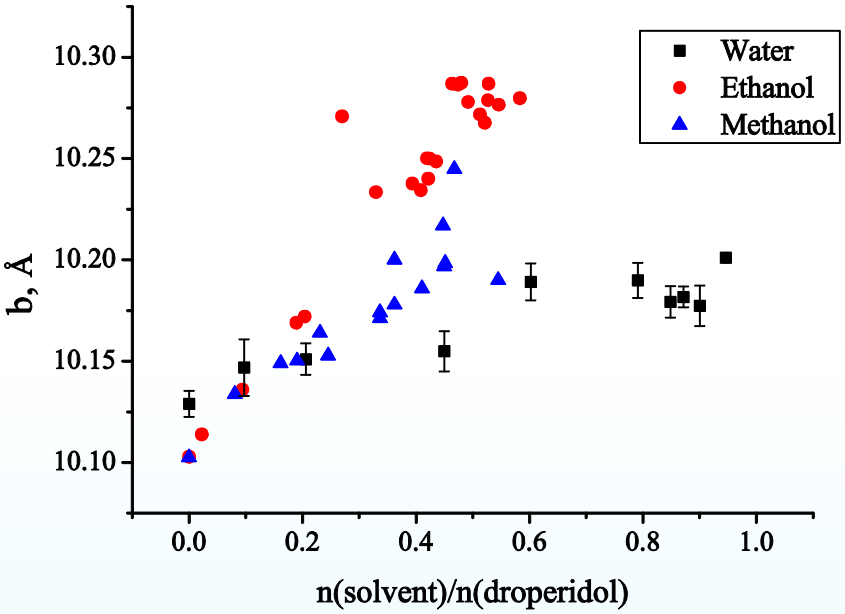


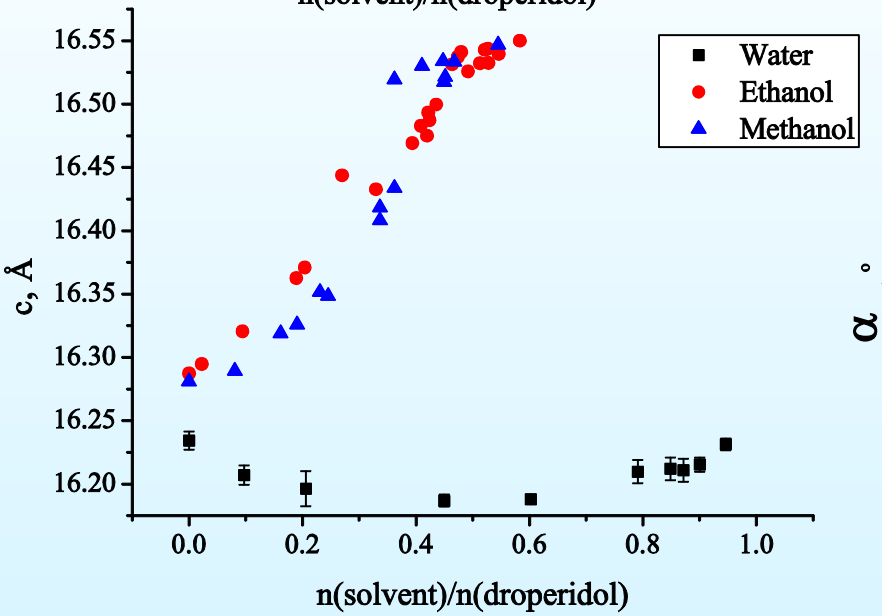
PXRD pattern change and crystal structure

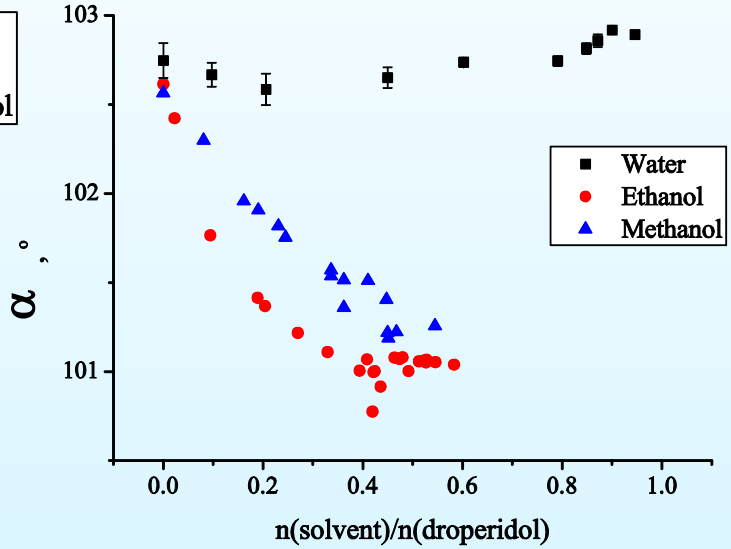


Lattice parameter changes

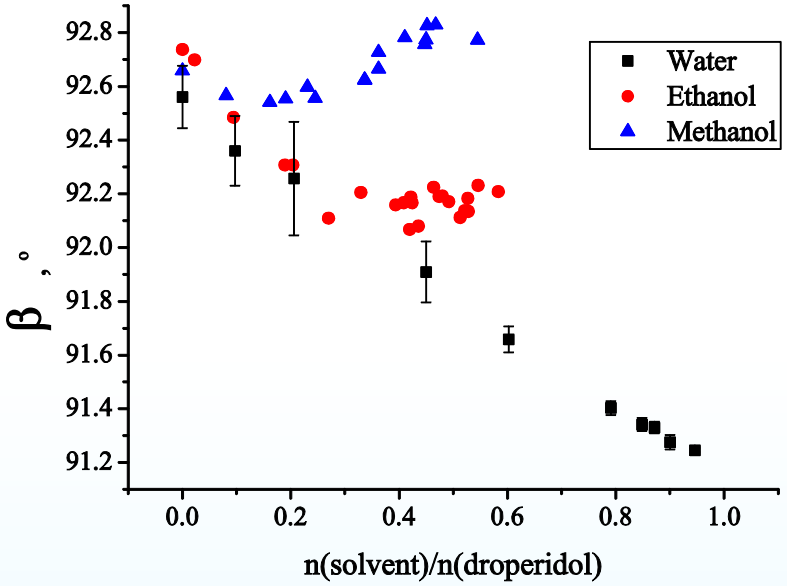


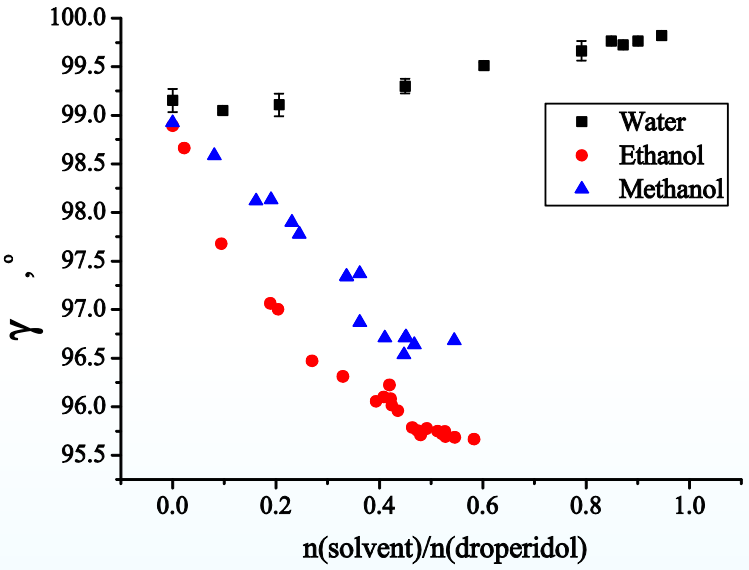


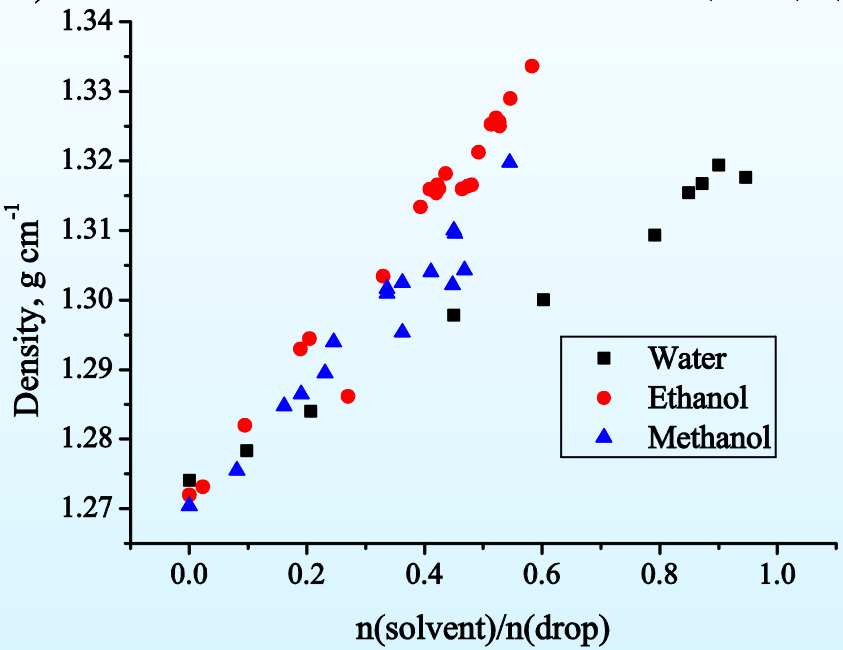




Lattice parameter changes







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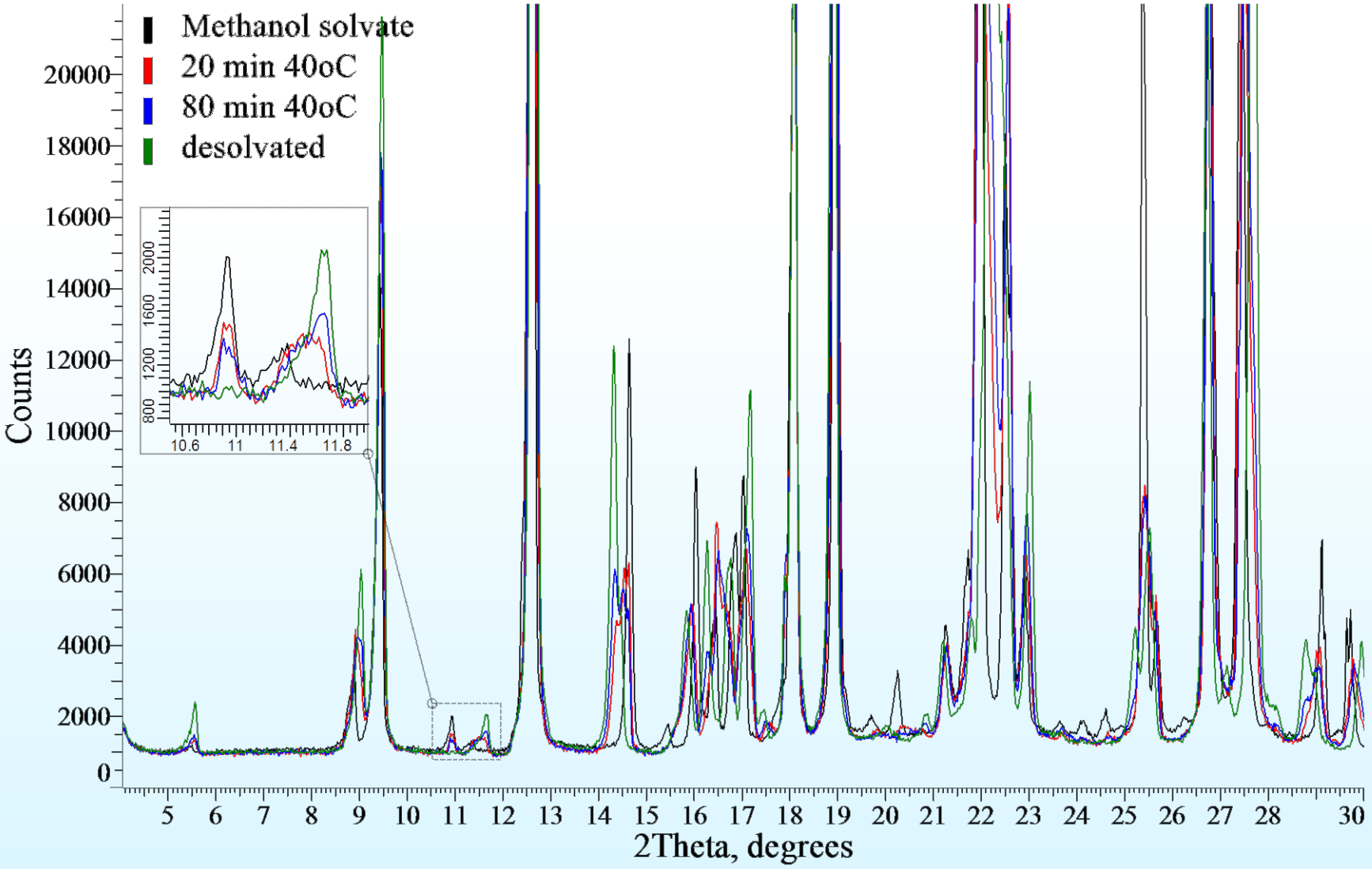
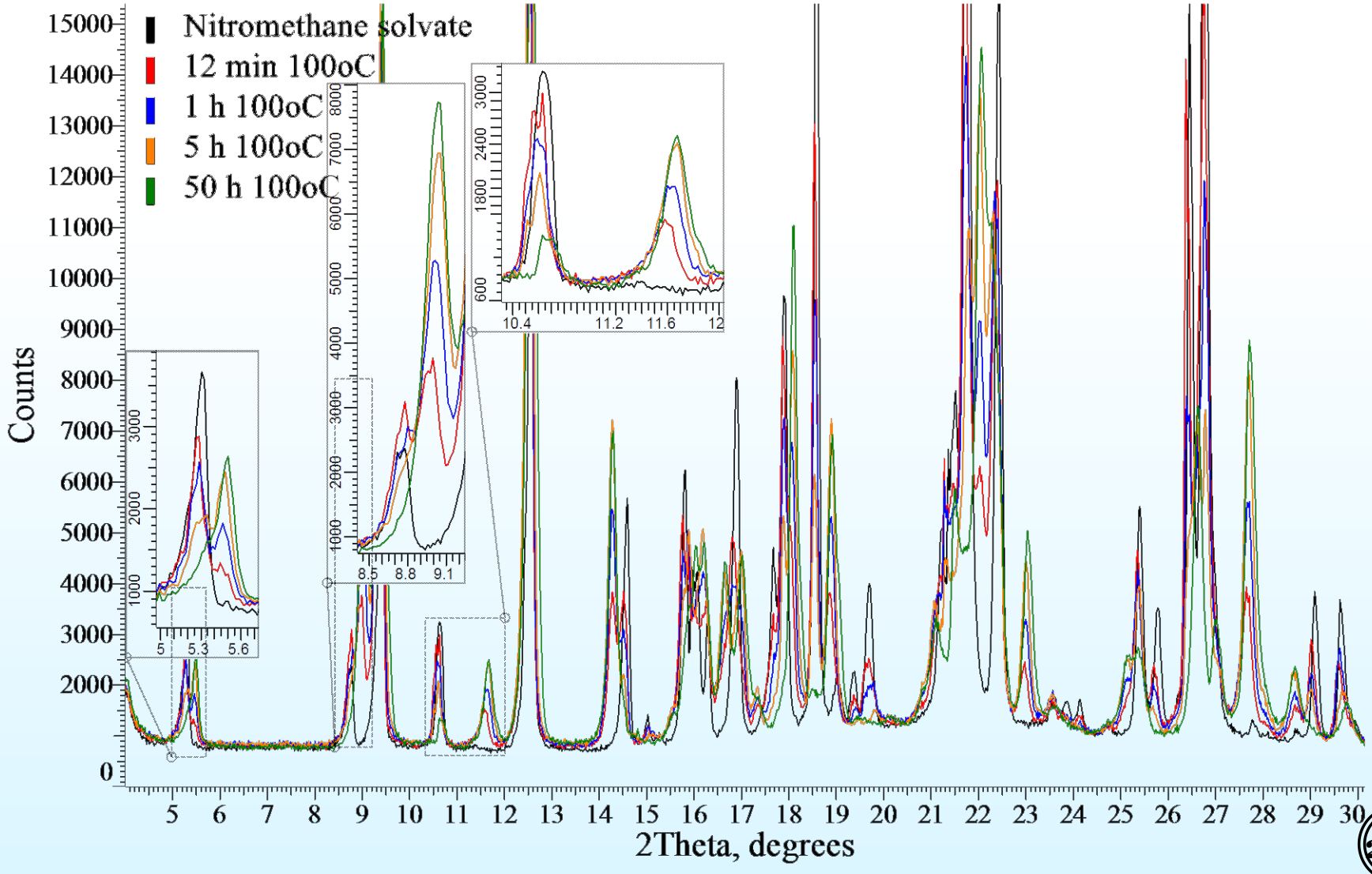
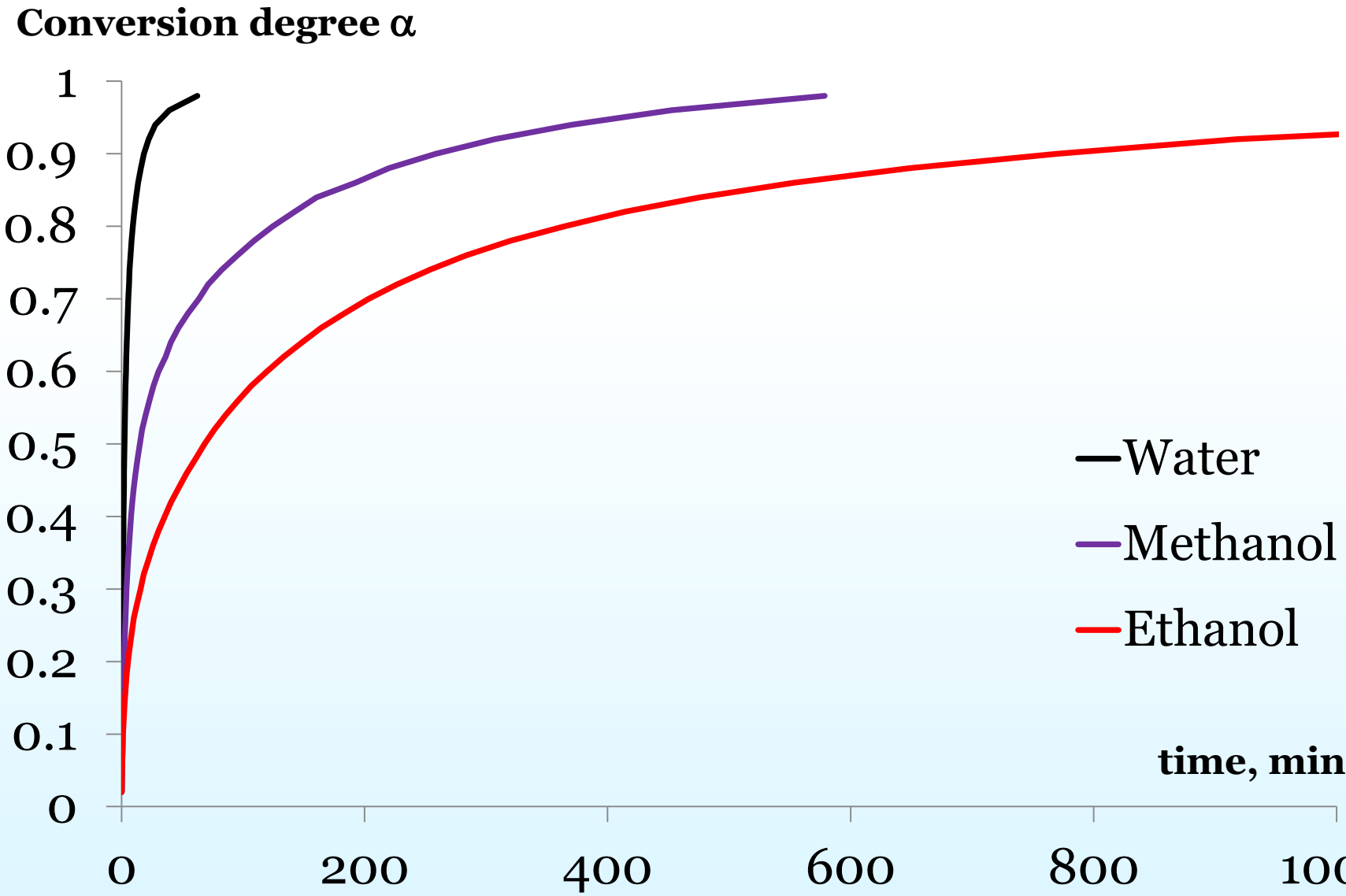
Desolvation in air – methanol solvate



Desolvation in air– nitromethane solvate



Desolvation kinetics in nitrogen flow



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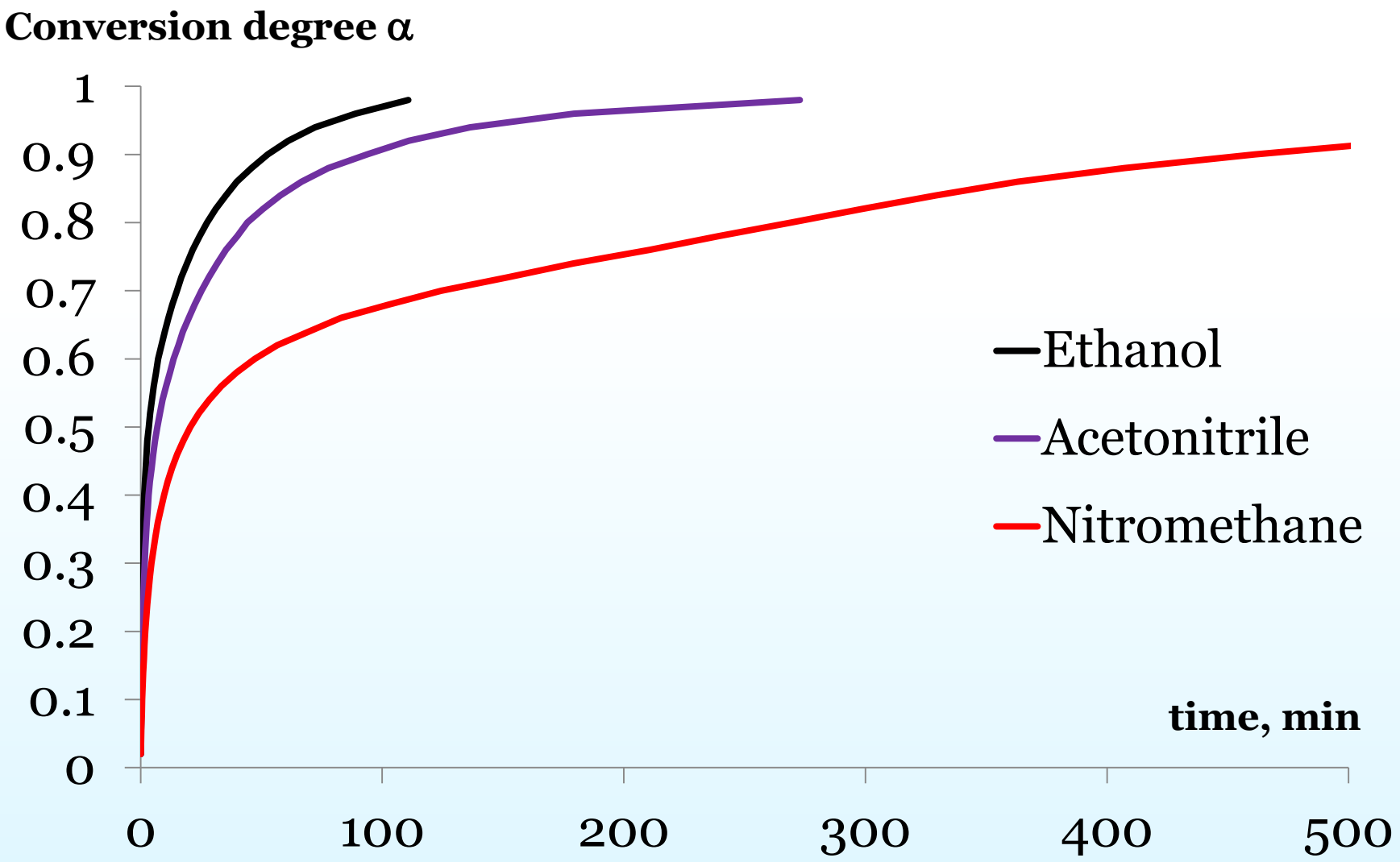

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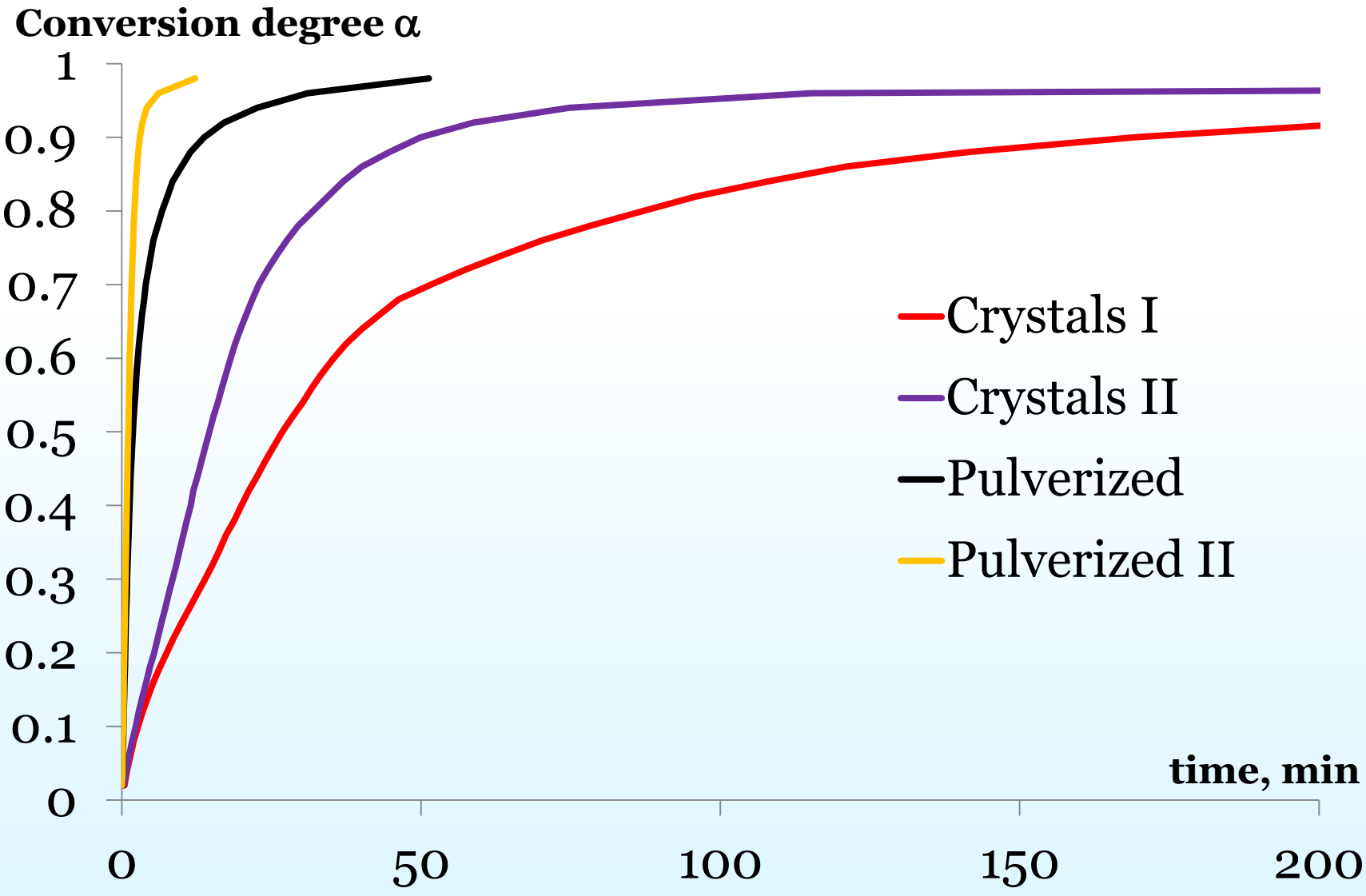
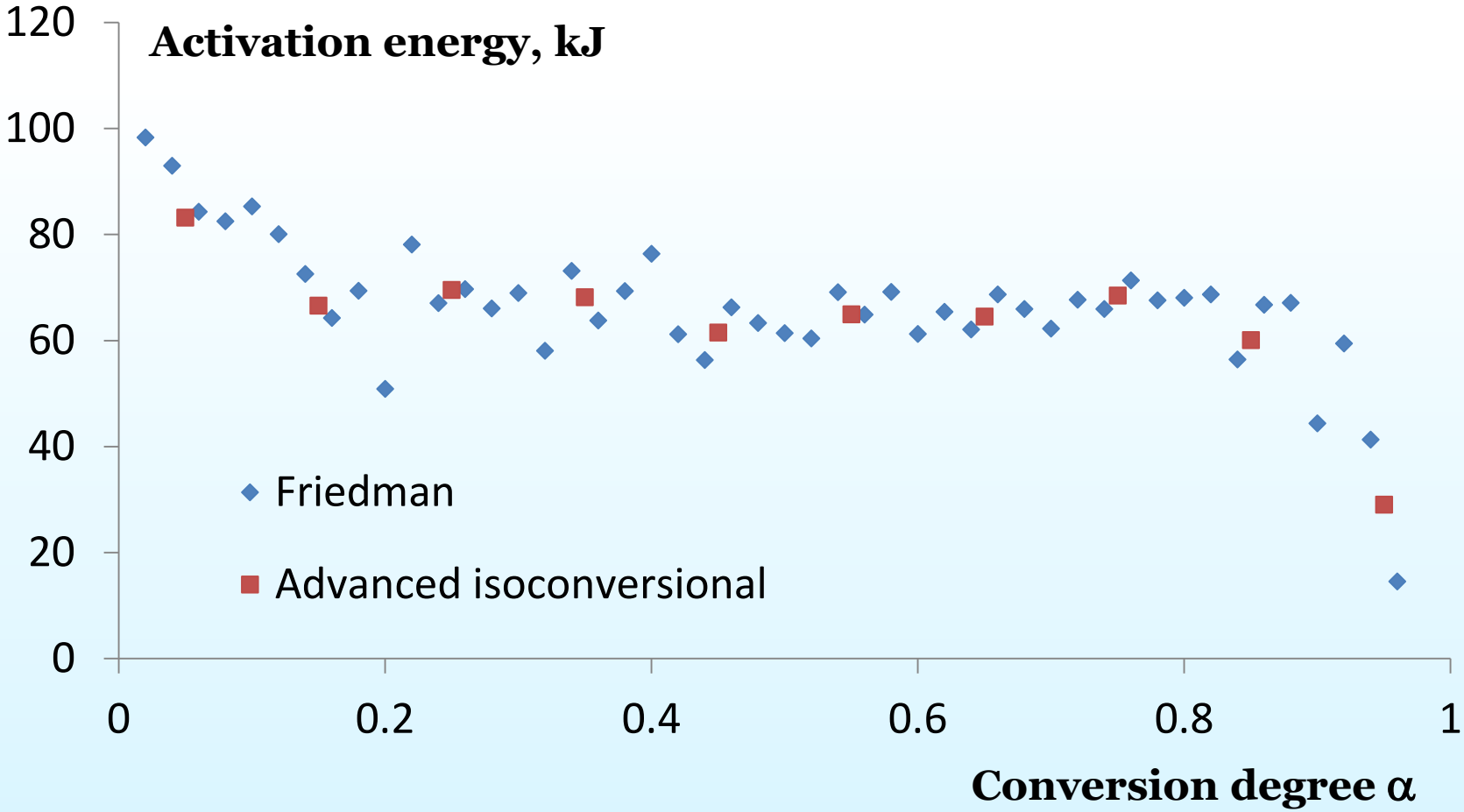


Kinetic parameter calculation

- Model free approach:
  - Calculation of activation energy by isoconversional methods
  - Kinetic model determination



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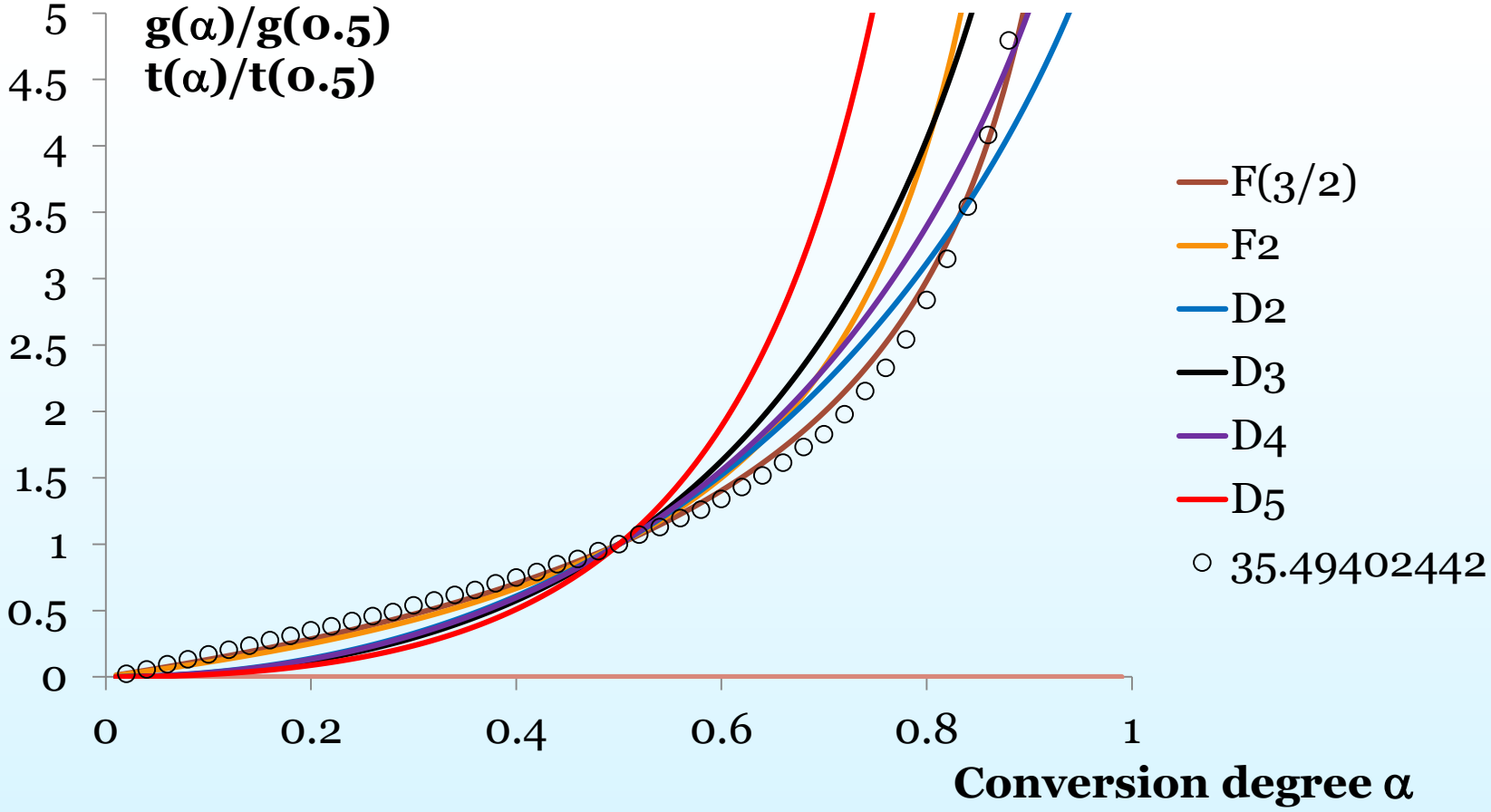

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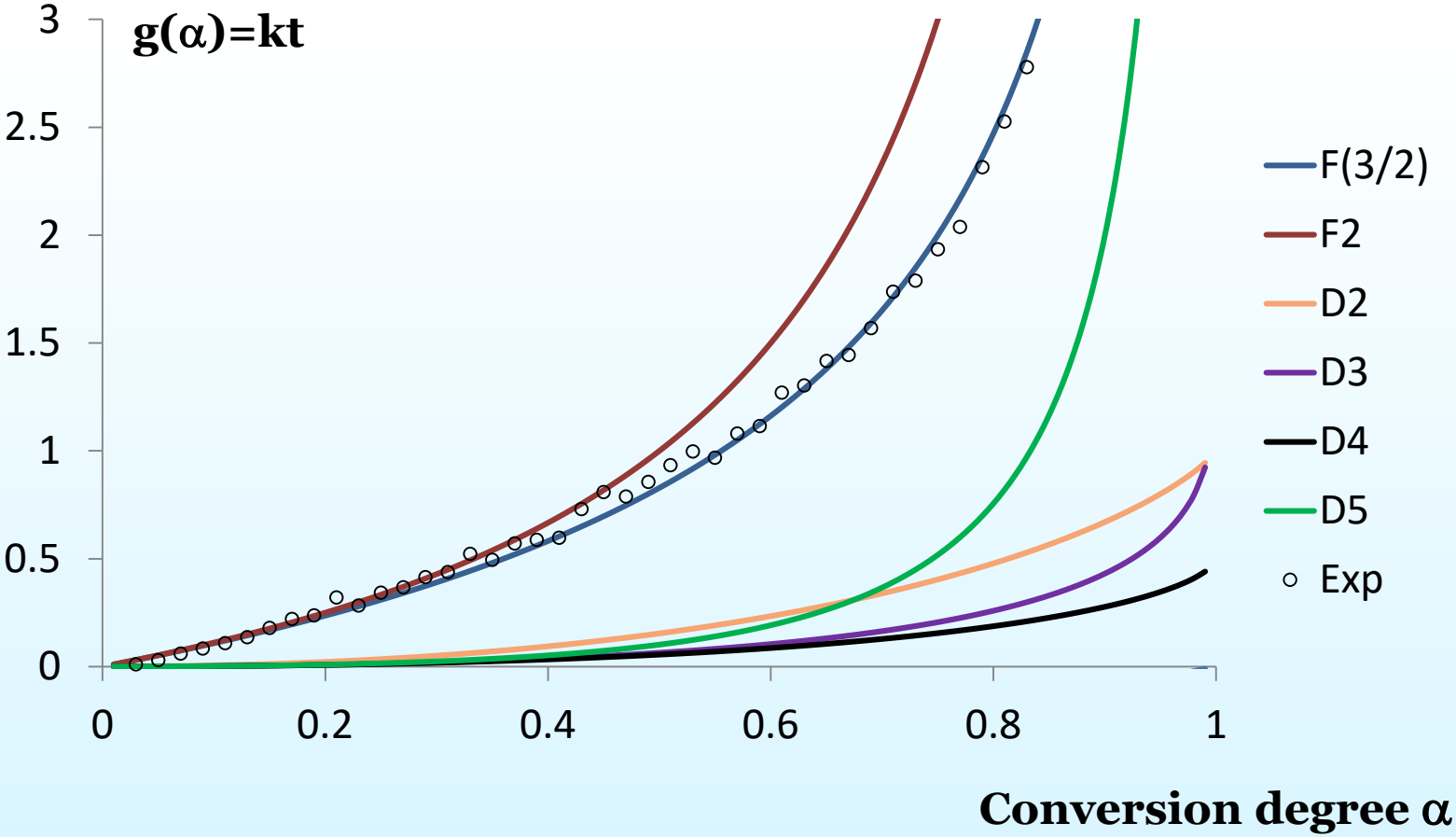
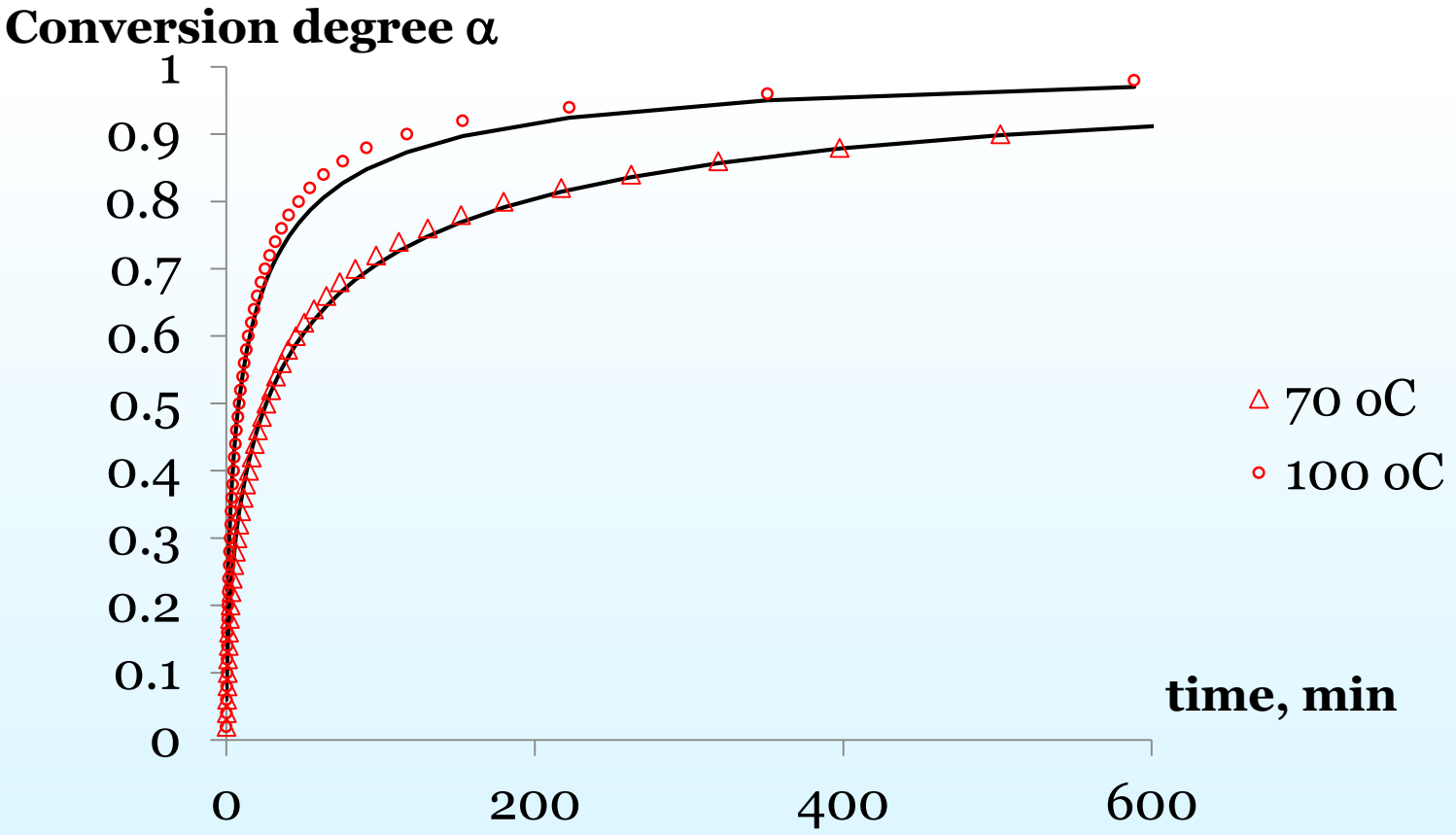
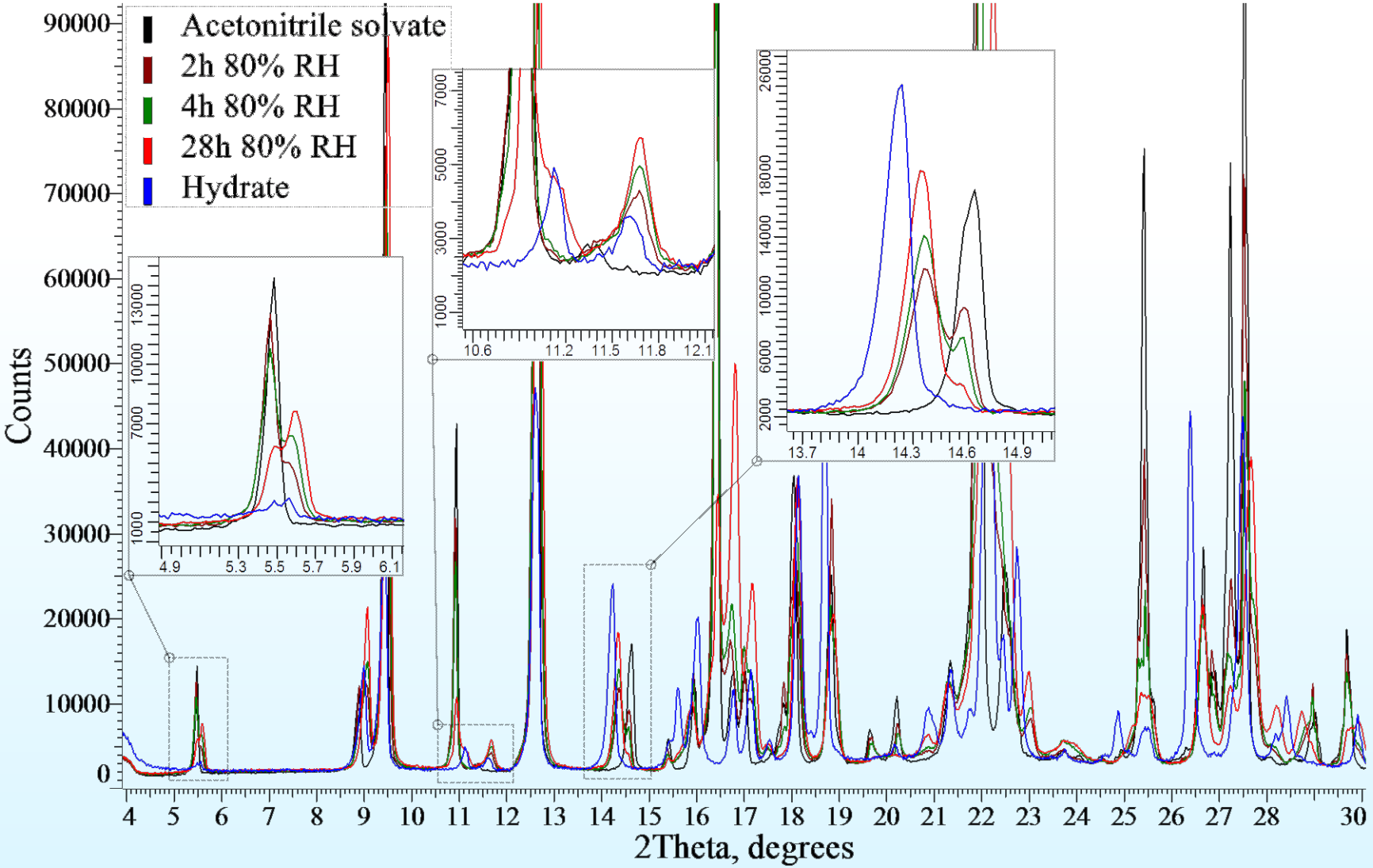


Kinetic parameter calculation

- Modelistic approach:
  - Kinetic model determination/selection
  - Calculation of rate constants and activation energy



Solvent exchange



Conclusions

- Droperidol forms isostructural solvates with water, ethanol, methanol, acetonitrile, nitromethane, chloroform and dichloromethane.
- Systematic lattice parameter change depending on solvent content was observed for water, ethanol and methanol.
- Desolvation kinetic was analysed. Kinetic model based on diffusion mechanism should be used.

Thank you for your attention!

Acknowledgments:

- **European Social Fund for a scholarship to A. Bērziņš and Latvian Academy of Sciences Grant.**
- **JSC Grindeks for droperidol samples**