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Structural Characterization and Rationalization of Formation, Stability, and Transformations of Benperidol Solvates

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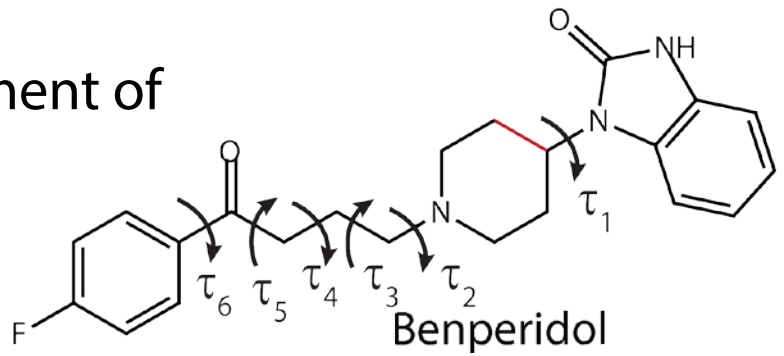
Outline

- Screening and characterization of benperidol solvates (crystalline forms)
  - Introduction
  - Solvate screening and physiochemical characterization
  - Structural characterization of the solvates
  - A study of the desolvation process
  - Rationalization of the solvate formation
- Benperidol vs. droperidol
  - Comparison of the obtained
  - Explanations for different crystal structures

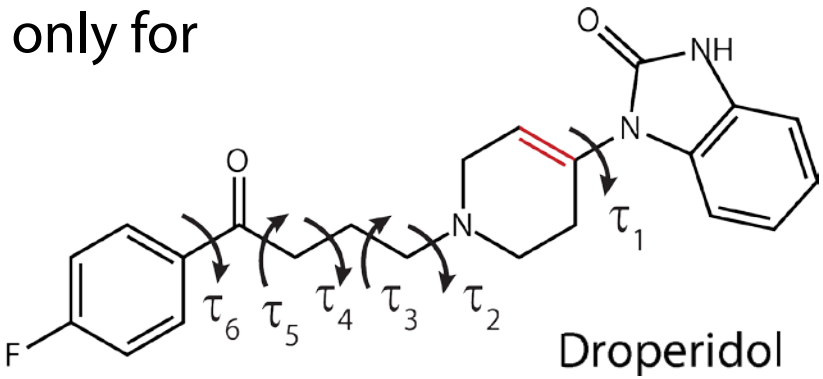
Introduction

- Benperidol:
  - an antipsychotic, used for the treatment of schizophrenia and to control anti-social, hypersexual behavior.
  - Reported to exist in 3 polymorphs (I, II and III), a dihydrate **DH** and an ethanol solvate $\mathbf{S_{Et}}$[1,2].
  - Crystal structure has been reported only for polymorph **I**[3].



Benperidol

- However:
  - is a promiscuous solvate former,
  - very similar API droperidol forms 11 solvates[4], including 7 isostructural solvates[4,5]



Droperidol

[1] - Azibi, M.; Draguet-Brughmas, M.; Bouche, R. *Pharm. Acta Helv.* **1982**, 57, 182.
[2] - Gassim, A. E. H.; Girgis Takia, P.; James, K. C. *Int. J. Pharm.* **1986**, 34, 23.
[3] - Declercq, J. P.; Germain, G.; Koch, M. H. J. *Acta Crystallogr., Sect. B* **1973**, 29, 2311.
[4] – Bērziņš, A.; Skarbulis, E.; Rekis, T.; Actiņš, A. *Cryst. Growth Des.* **2014**, 14, 2654.
[5] – Bērziņš, A.; Rekis, T.; Actiņš, A. *Cryst. Growth Des.* **2014**, 14, 3639.

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Solvate screening

Solvent	Classification[1]	Group[2]	Obtained phase
n-hexane, *n*-heptane	AAA	1	**I**
CCl_4	HBD	1	**(S_{TCC})**
EtOAc	AP	2	**I/S_{EtOAc}**
BuOAc, *i*-PrOAc	AP	2	**I**
THF	EPD	2	**I**
tert-BME	EPD/AAA	2	**I**
1-butanol, 1-propanol, isobuthanol	HBD	3	**I**
2-propanol	HBD	3	**I/II**
ethanol	HBD	3	**S_{Et}**
methanol	HBD	3	**S_{Me}**
toluene, *o*-xylene	AALP	4	**I/HH**
acetone, cyclohexanone, butanone, 3-pentanone	AP	5	**I**
DMF	AP	6	**I**
dimethylsulfoxide	AP	6	no crystallization
$CHCl_3$	EPD/HBD/AP	7	**(S_{CLF})**
CH_2Cl_2, 1,1-dichloroethane	AP	7	**I**
acetonitrile	AP	9	**S_{ACN}/I**
nitromethane	AP	9	**I/S_{NM}**
benzyl alcohol	AALP	10	**S_{Benz}**
1,4-dioxane	AP/EPD	11	**S_{DIOX}**
water	HBD	15	**DH**
cyclohexanol	HBD	-	**I**

[1] – Classification according to: Gramatica, P.; Navas, N.; Todeschini, R. *Trends Anal. Chem.* **1999**, 18, 461.
AP = aprotic polar, AALP = aromatic apolar or lightly polar, EPD = electron pair donors, HBD = hydrogen bond donors, AAA = aliphatic aprotic apolar.

[2] - Groups are based on cluster analysis of following solvent parameters: hydrogen bond acceptor propensity, hydrogen bond donor propensity, polarity/dipolarity, dipole moment, and dielectric constant according to: Gu, C.-H.; Li, H.; Gandhi, R. B.; Raghavan, K. *Int. J. Pharm.* **2004**, 283, 117.

Physiochemical characterization of solvates

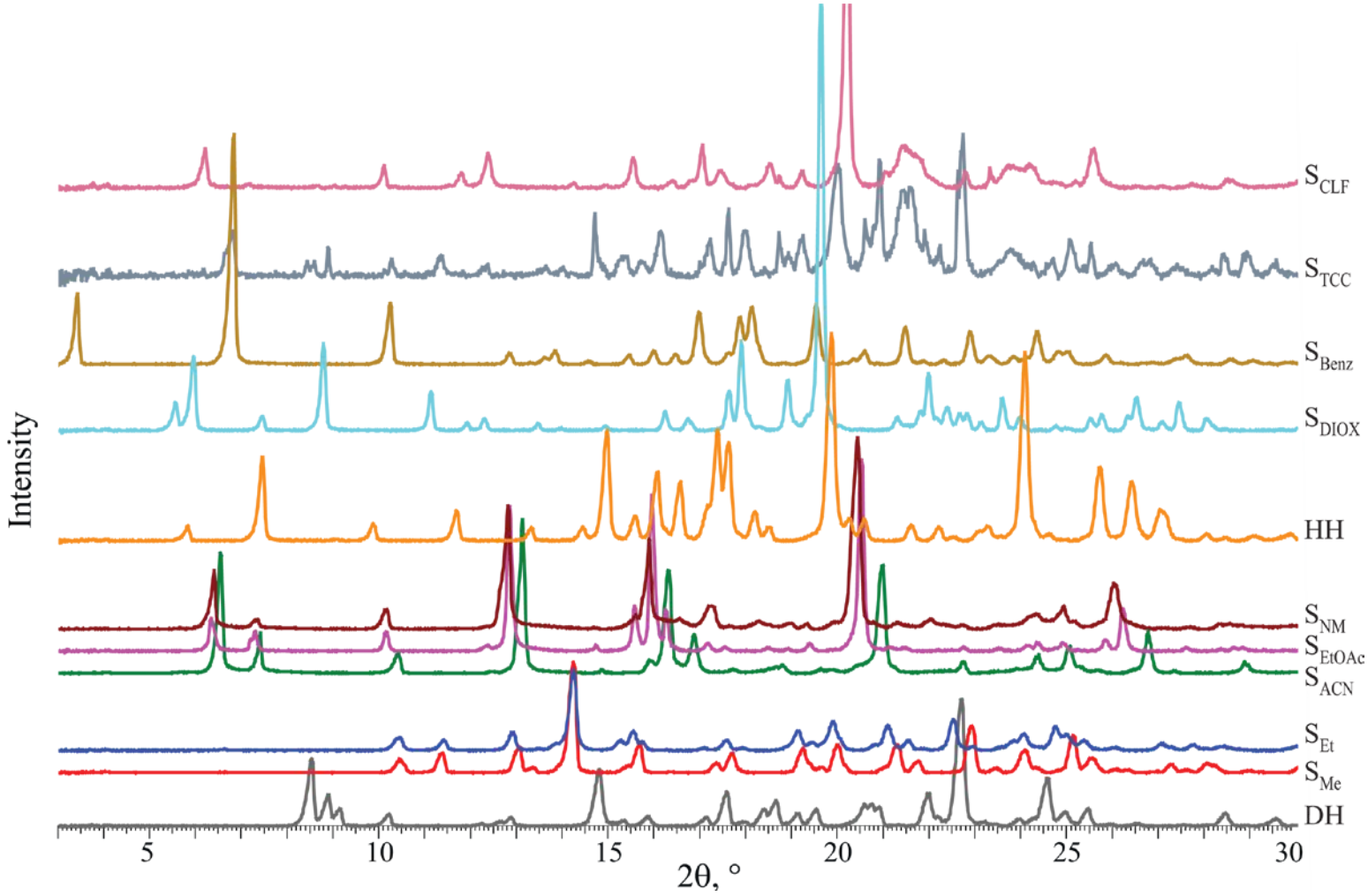

Figure 1. PXRD patterns of the benperidol solvates.

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Physiochemical characterization of solvates

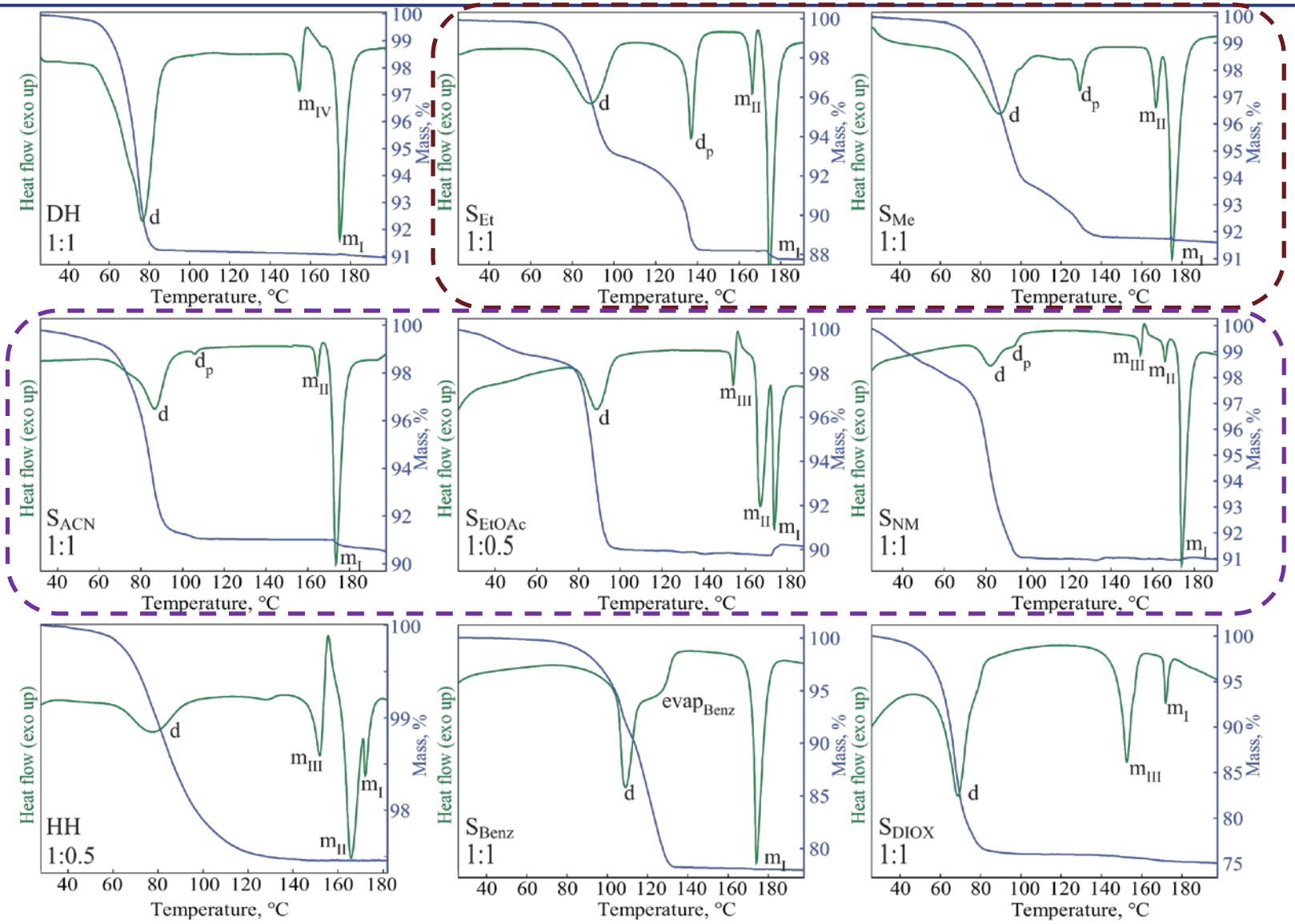

Figure 2. The DTA and TG curves of benperidol solvates.

Desolvation products

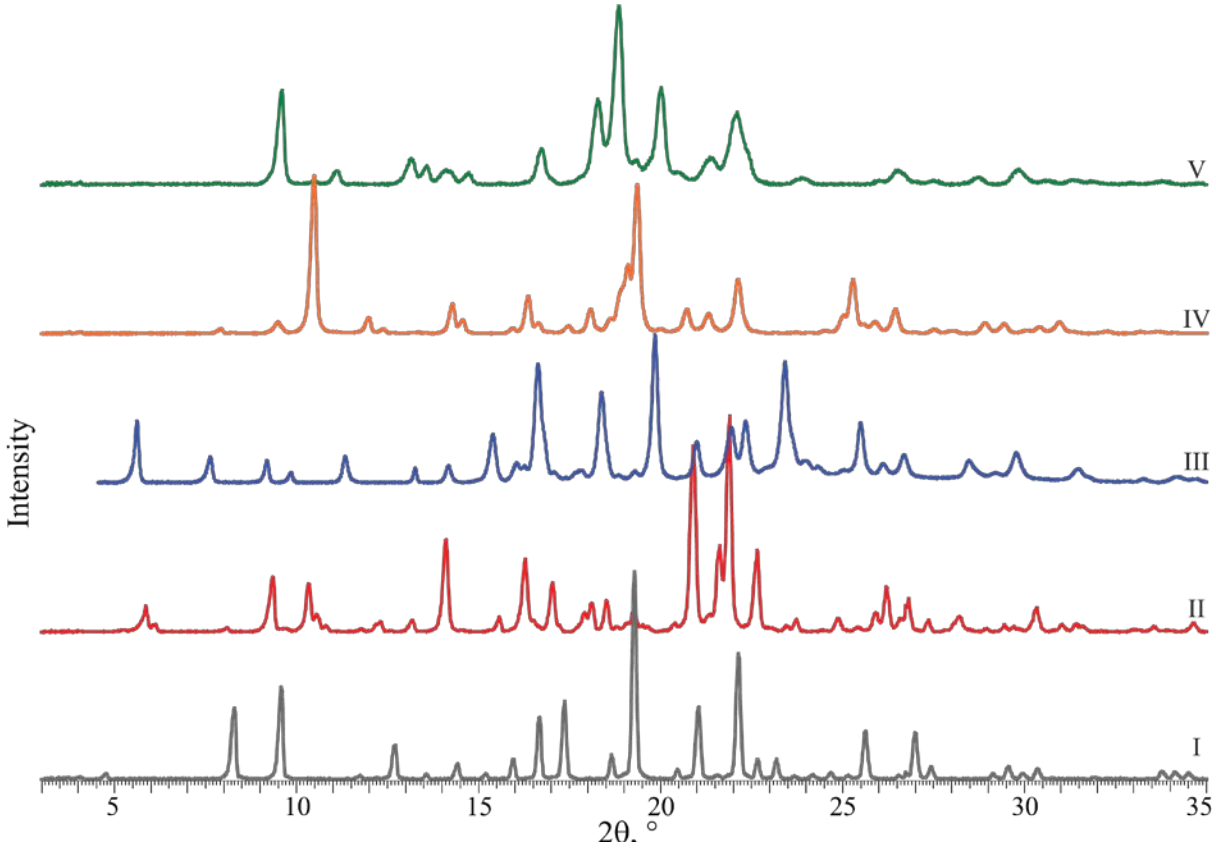

Figure 3. PXRD patterns of the benperidol polymorphs.

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Determination of crystal structures

Table 1. Crystallographic data for the benperidol phases .

Solvate	II	DH	S_{Et}	S_{Me}	S_{ACN}	S_{EtOAc}	HH	S_{Benz}	III
Crystal system	triclinic	monocl.	monocl.	monocl.	triclinic	triclinic	monocl.	orthor.	triclinic
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$C2/c$	$Pbca$	$P\bar{1}$
a (Å)	10.8417	11.0595	15.0684	15.1097	5.56500	5.4228	36.7342	13.7193	15.61501
b (Å)	16.2903	9.3896	10.8602	10.7200	14.1256	14.6014	5.58581	51.6467	11.48189
c (Å)	17.9497	20.4456	15.2555	15.3070	15.0478	14.8045	23.6629	7.43071	5.45694
α (°)	66.7233	90	90	90	109.2583	109.936	90	90	86.627
β (°)	87.0069	91.7206	117.6353	119.3538	90.9875	90.199	124.8680	90	96.618
γ (°)	85.0074	90	90	90	100.071	100.322	90	90	94.435
V (Å^3)	2900.55	2122.20	2211.69	2161.04	1095.91	1081.50	3983.71	5265.07	967.71
Z/Z′	6/3	4/1	4/1	4/1	2/1	2/1	8/1	8/1	2/1
T, K	173(2)	173(2)	173(2)	173(2)	173(2)	100(2)	298(3)	298(3)	298(3)
GOF	1.013	1.243	1.028	0.972	1.018	1.030			
R_{wp}							0.02897	0.03356	0.03686
Pacing coef.	0.682	0.689	0.684	0.672	0.681	0.690	0.675	0.651	0.681

Determination of crystal structures

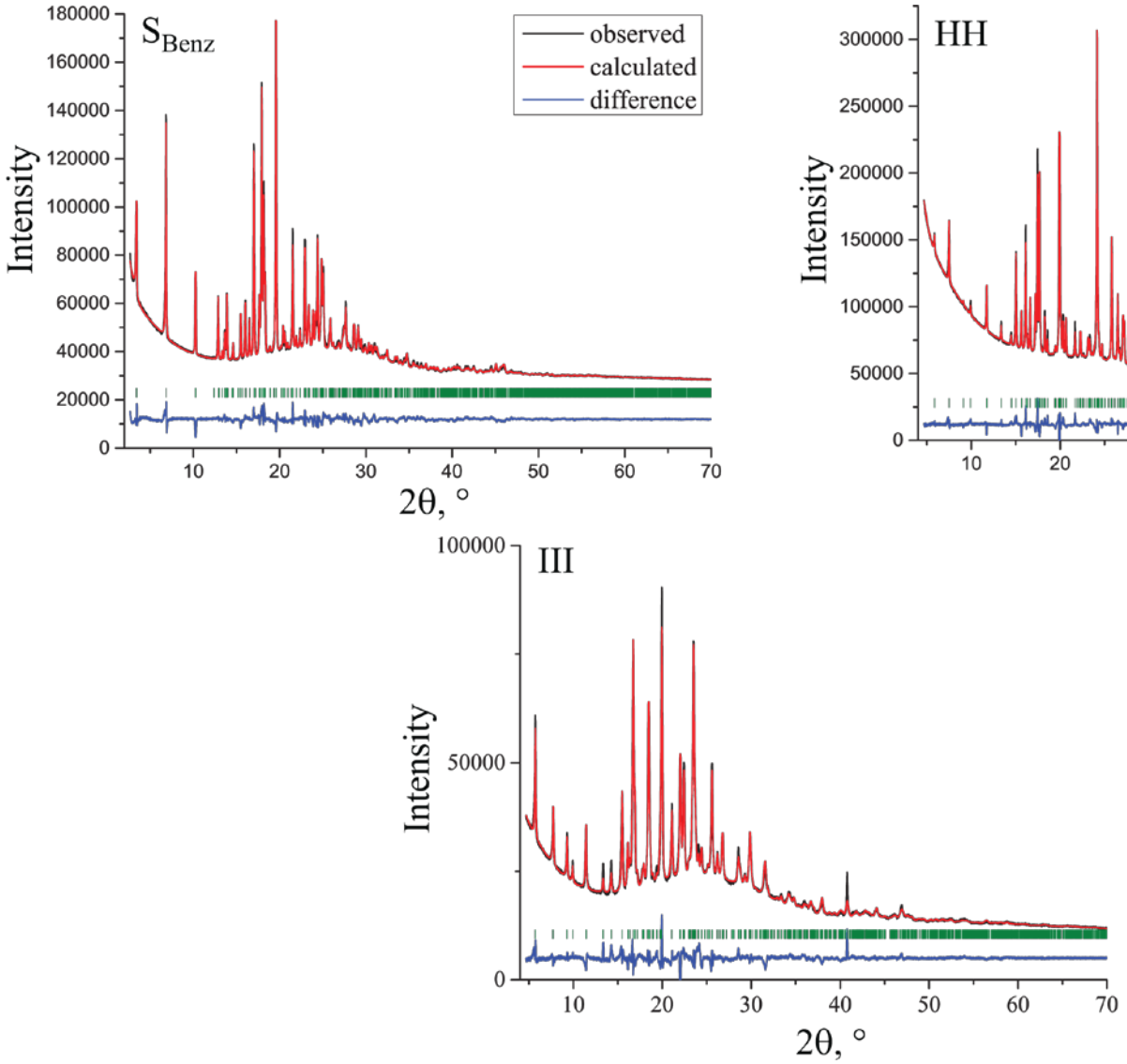

Figure 4. PXRD profiles from the final Rietveld refinement of various benperidol forms.

Determination of crystal structures

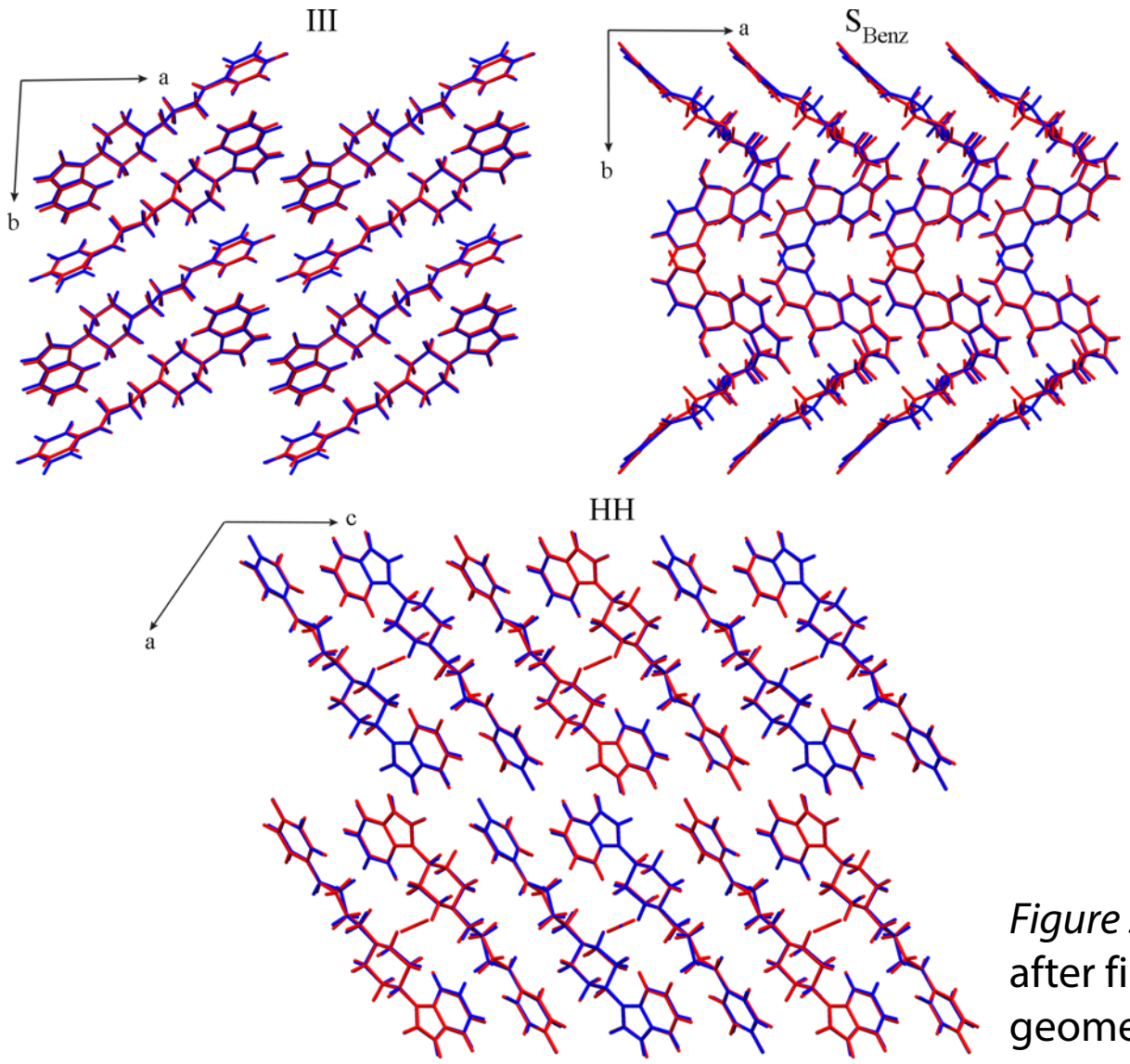

Figure 5. Overlay of crystal structures after final Rietveld refinement and geometry optimization in CASTEP.

Crystal structure analysis

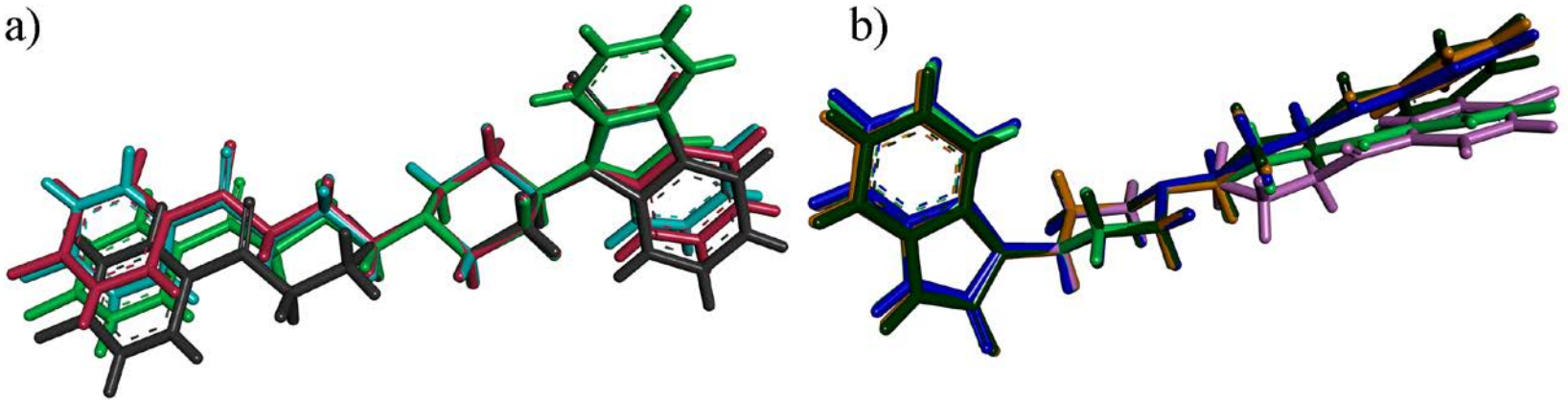

Figure 6. An overlay of benperidol molecules in a) polymorphs; b) solvates and polymorph I.

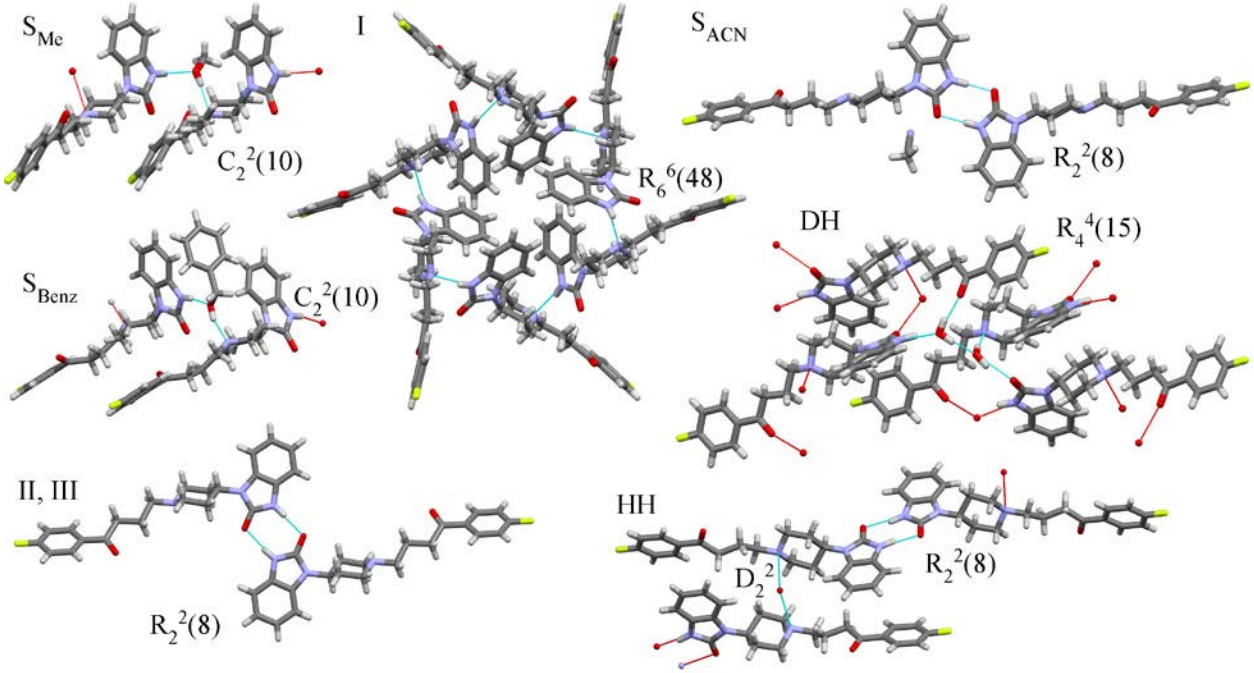

Figure 7. Hydrogen bond patterns observed in crystal forms of benperidol.

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Crystal structure analysis

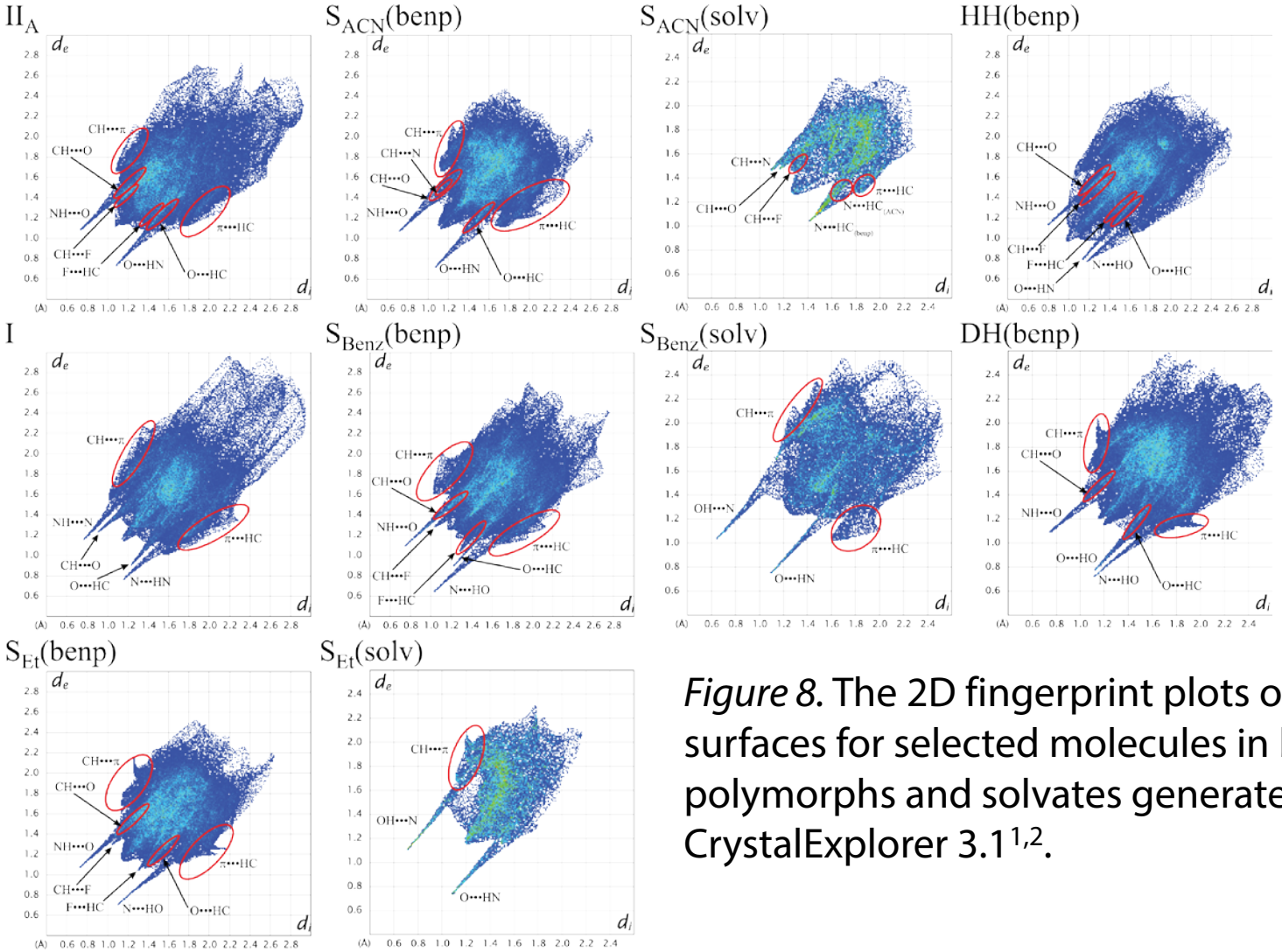

Figure 8. The 2D fingerprint plots of Hirshfeld surfaces for selected molecules in benperidol polymorphs and solvates generated using CrystalExplorer 3.1[1,2].

[1] - McKinnon, J. J.; Jayatilaka, D.; Spackman, M. A. *Chem. Commun.* **2007**, 3814.
[2] - Spackman, M. A.; Jayatilaka, D. *CrystEngComm* **2009**, 11, 19.

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Crystal structure analysis

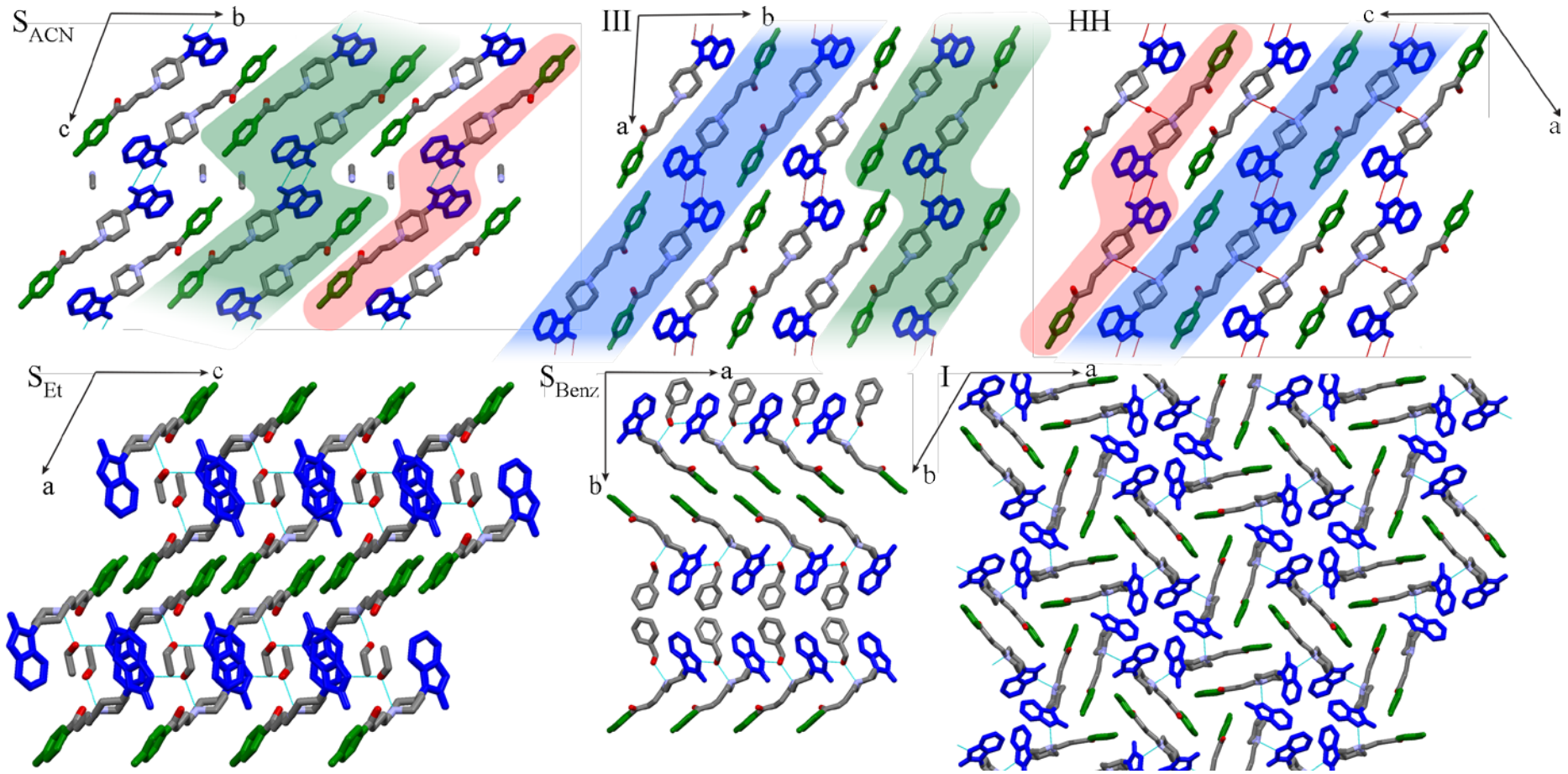

Figure 9. Molecular packing in benperidol polymorphs and solvates. Identical supramolecular constructs were identified using XPac code[1,2].

[1] - Gelbrich, T. *IUCr Newslett.* **2006**, 39.
[2] - Gelbrich, T.; Hursthouse, M. B. *CrystEngComm* **2005**, 7, 324.

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Crystal structure analysis

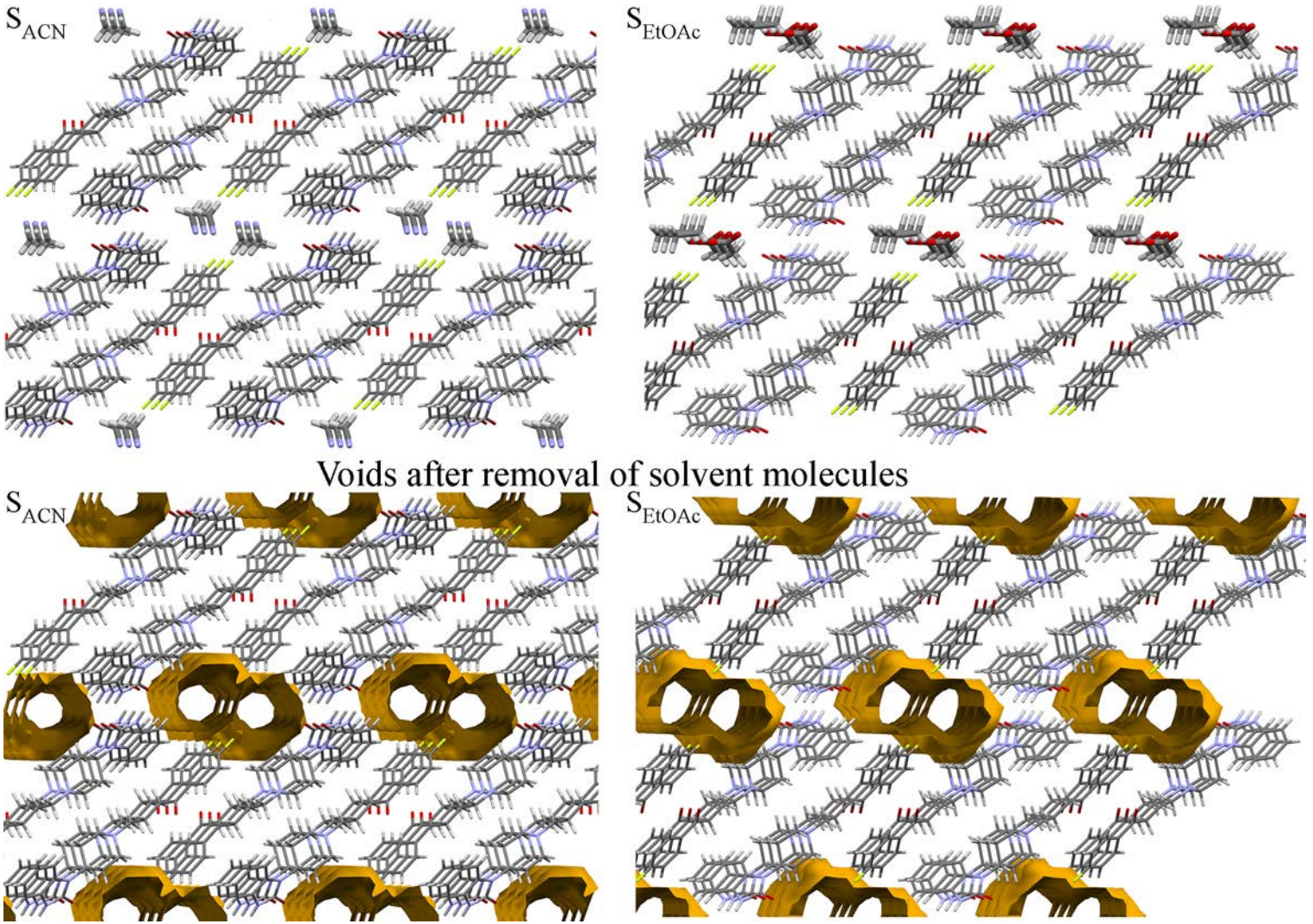

Figure 10. Arrangement of solvent molecules in the channels of type 2 solvates.

Desolvation process and products

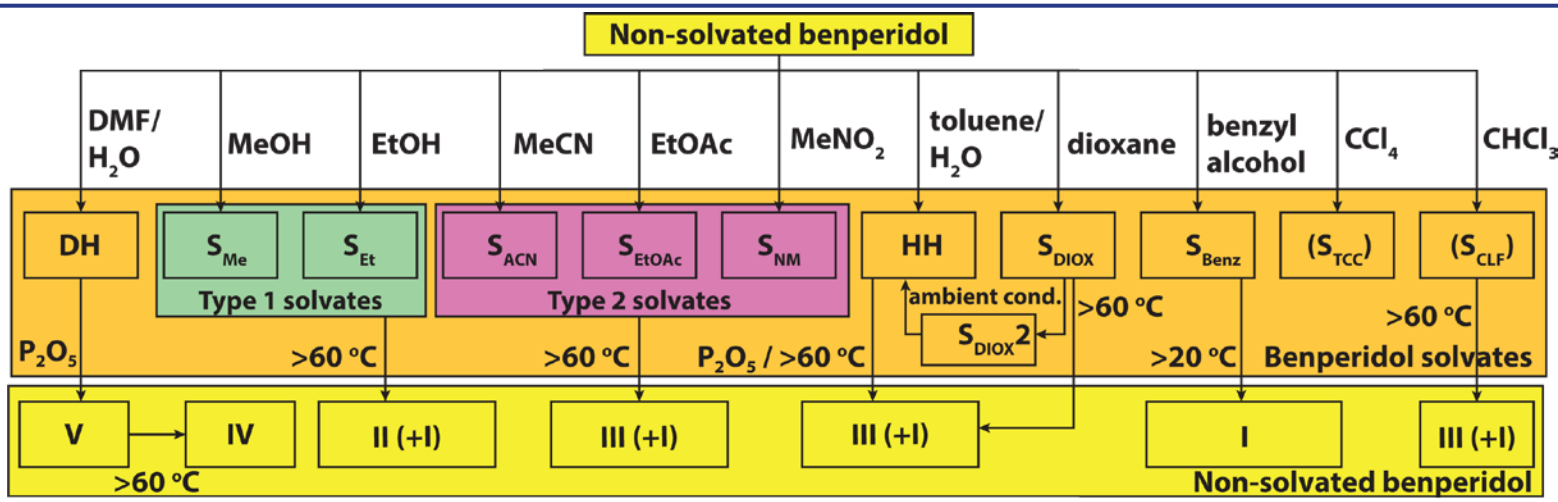

Figure 11. A schematic representation of benperidol solvate preparation and the phase transformations occurring during their desolvation.

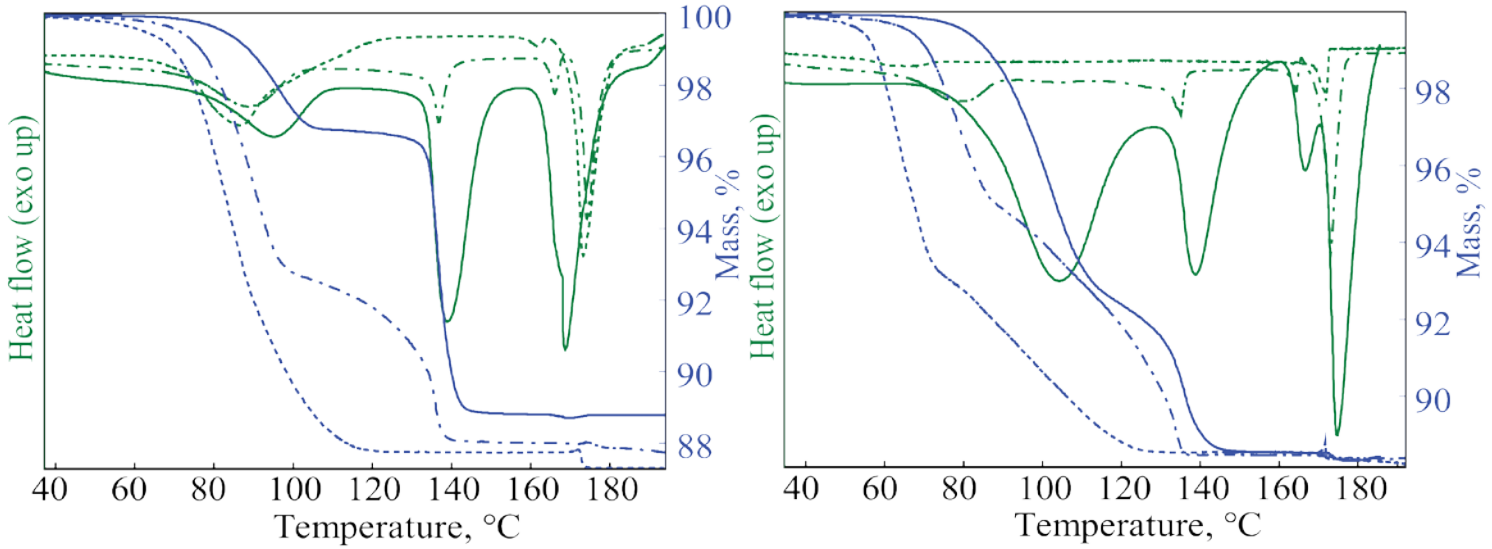

Figure 12. The effect of particle size and the heating rate on the desolvation of **S_{Et}**.

Desolvation process and products

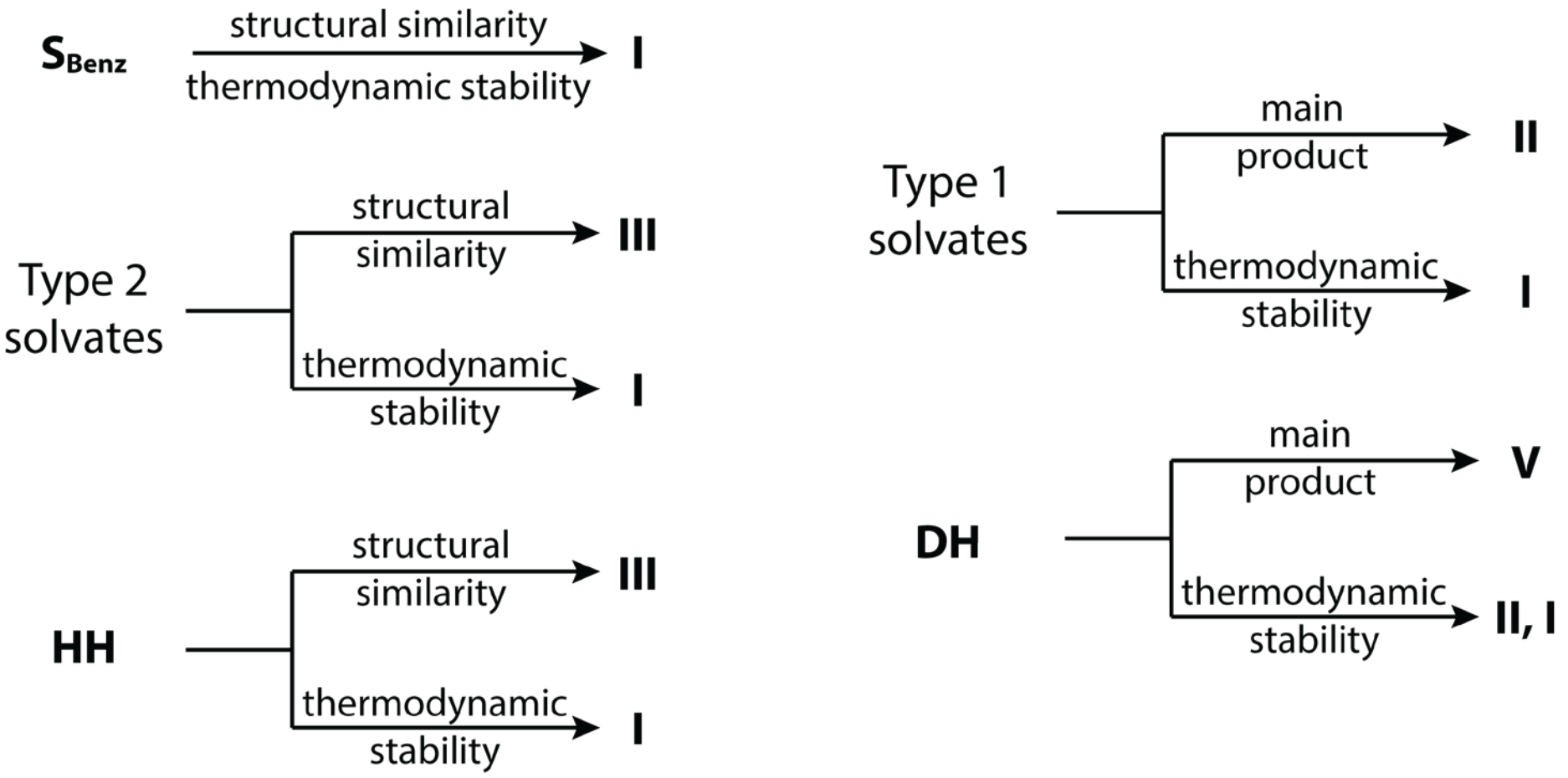

Figure 13. A schematic representation of the driving forces for the phase transformations occurring during the desolvation of benperidol solvates.

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Analysis of solvate formation

Solvent	Classification[1]	Group[2]	Obtained phase
n-hexane, *n*-heptane	AAA	1	**I**
CCl_4	HBD	1	**(S_{TCC})**
EtOAc	AP	2	**I/S_{EtOAc}**
BuOAc, *i*-PrOAc	AP	2	**I**
THF	EPD	2	**I**
tert-BME	EPD/AAA	2	**I**
1-butanol, 1-propanol, isobuthanol	HBD	3	**I**
2-propanol	HBD	3	**I/II**
ethanol	HBD	3	**S_{Et}**
methanol	HBD	3	**S_{Me}**
toluene, *o*-xylene	AALP	4	**I/HH**
acetone, cyclohexanone, butanone, 3-pentanone	AP	5	**I**
DMF	AP	6	**I**
dimethylsulfoxide	AP	6	no crystallization
$CHCl_3$	EPD/HBD/AP	7	**(S_{CLF})**
CH_2Cl_2, 1,1-dichloroethane	AP	7	**I**
acetonitrile	AP	9	**S_{ACN}/I**
nitromethane	AP	9	**I/S_{NM}**
benzyl alcohol	AALP	10	**S_{Benz}**
1,4-dioxane	AP/EPD	11	**S_{DIOX}**
water	HBD	15	**DH**
cyclohexanol	HBD	-	**I**

Analysis of solvate formation

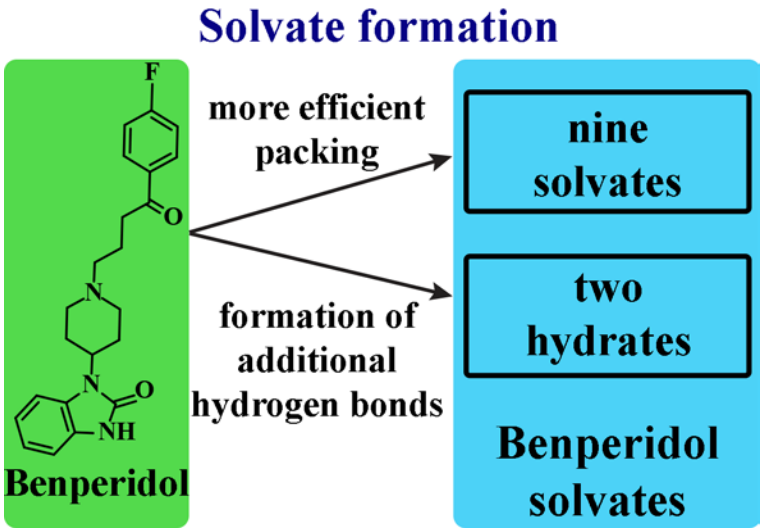

Figure 14. A schematic representation of the driving forces for the solvate formation of the benperidol.

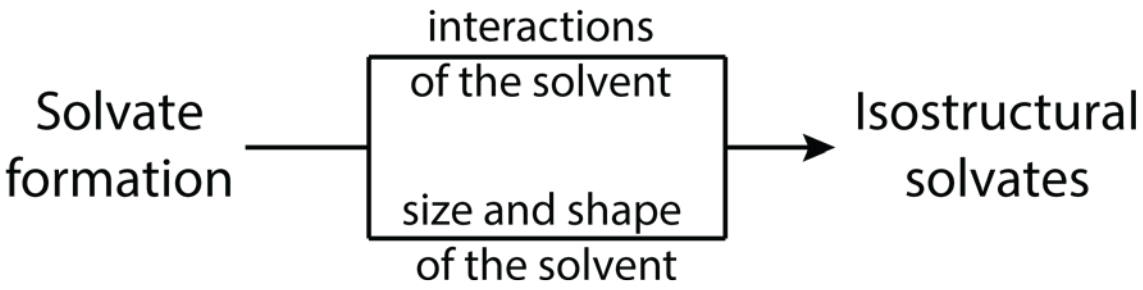

Figure 16. A schematic representation of the driving forces for the formation of the isostructural solvates of benperidol.

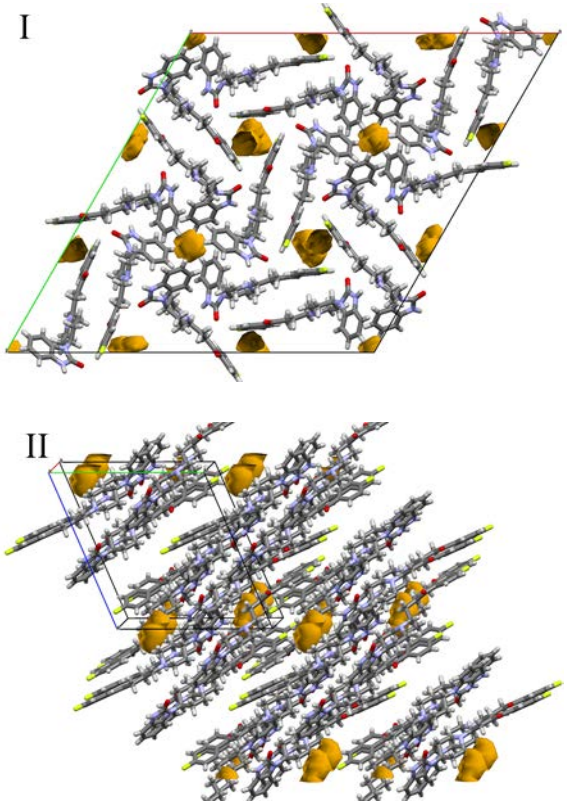

Figure 15. A representation of the voids in the crystal structures of benperidol polymorphs I and II.

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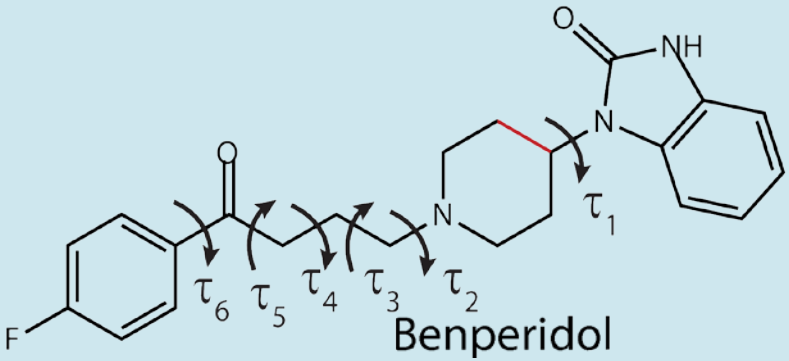
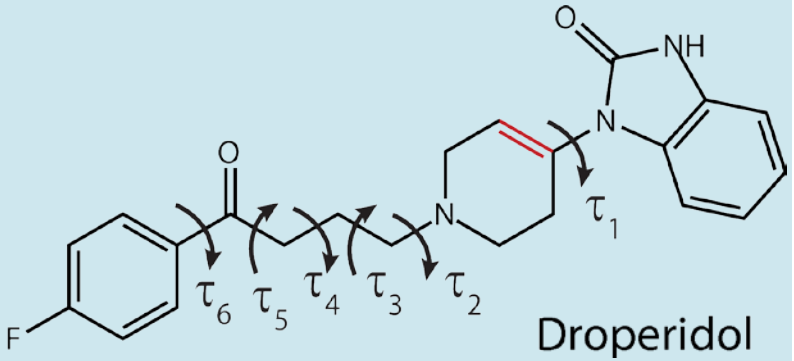
Conclusions

- Crystallization of benperidol from various solvents produced nine new solvates. The existence of a certain solvate, however, cannot guarantee its facile formation and discovery.
- The main reason for the formation of various benperidol crystal structures was the possibilities of diverse molecular packing, resulting in different intermolecular interactions.
- The desolvation products were determined through an interplay of structural similarity and thermodynamic stability of the resulting polymorphs.
- The inability of benperidol molecules to pack efficiently without solvent was the main reason for solvate formation, whereas the presence of different functional groups in benperidol molecule enabled the formation of a wide range of stable solvate structures containing various solvent molecules.
- The possible interactions and the size and shape of the solvent molecules were important factors in solvate formation.

These results have been published:

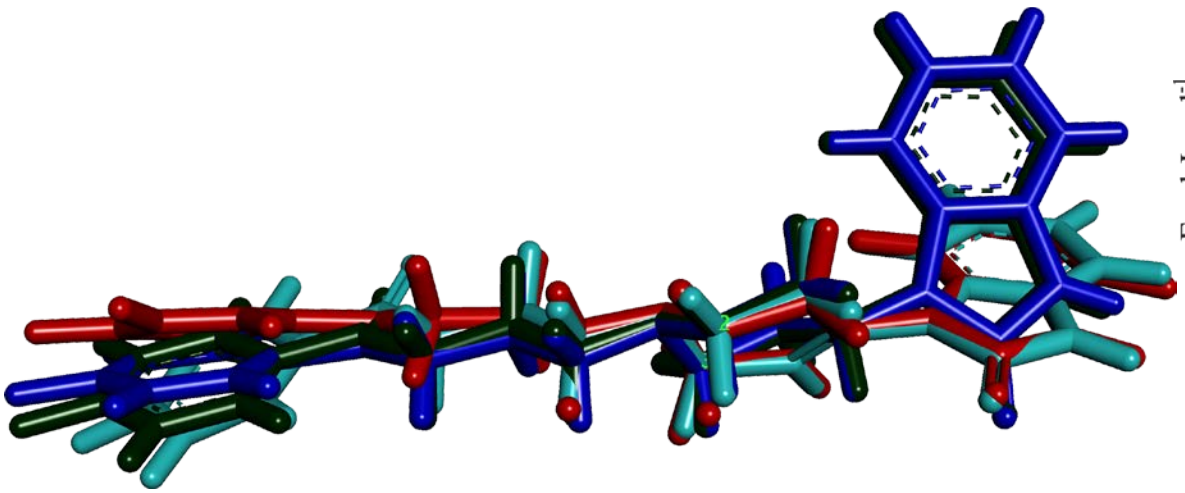
Bērziņš, A.; Skarbulis, E.; Actiņš, A. *Cryst. Growth Des.* **2015**, 15, 2337.

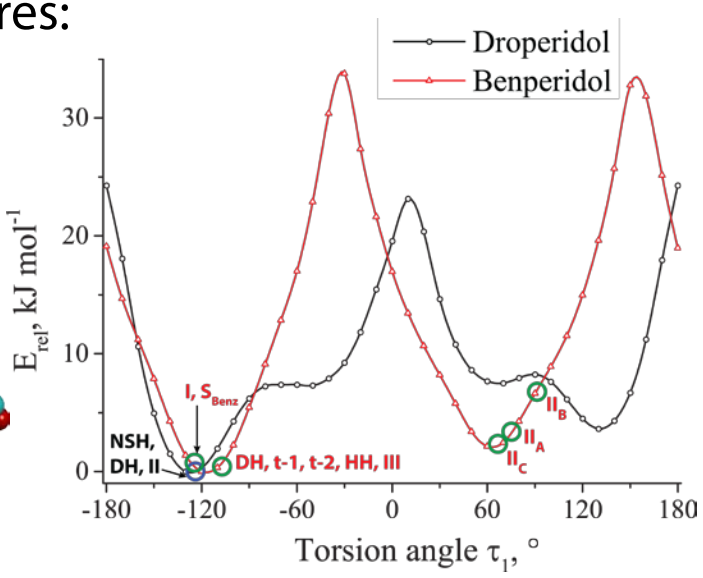
Comparison of benperidol and droperidol

Property	Benperidol	Droperidol
Molecular structure	 Benperidol	 Droperidol
Polymorphs	5 (**I** – **V**)	4 (**I** – **IV**)
Solvates	11 solvates: **DH** S_{Et} S_{Me} **HH** S_{DIOX} S_{Benz} S_{ACN} S_{NM} S_{EtOAc} S_{CLF} S_{TCC}	11 solvates: **NSH** S_{Et} S_{Me} S_{ACN} S_{NM} S_{CLF} S_{DCM} **DH** S_{DIOX} S_{TOL} S_{TCC}
	No isostructural phases	
Driving factors	More efficient packing. Formation of additional H-bonds (**DH**, **HH**).	More efficient packing. Formation of additional H-bonds (**DH**).

Comparison of benperidol and droperidol

- Possible reasons for formation of different structures:
  - Different conformation:





  - More efficient packing:

Phase	Benperidol → Droperidol		Droperidol → Benperidol	
	$\Delta E_{Lattice}$	ΔE_{Total}	$\Delta E_{Lattice}$	ΔE_{Total}
II	11.6	9.1	-7.2	0.5
DH	10.7	11.4	9.0	11.1
S_{Me}	38.8	43.6	-30.6	-20.2
S_{Et}	49.4	56.3	-43.5	-35.3
S_{ACN}	25.1	35.9	-14.9	-11.8

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