RAPID SOLID-STATE NMR-DRIVEN CRYSTAL STRUCTURE DETERMINATION OF TAUTOMERIC SYSTEMS

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AIM OF THE WORK

SSNMR + CRYSTAL STRUCTURE PREDICTION
=
CSP-NMR CRYSTALLOGRAPHY[1]
Exploits SSNMR information in
INPUT and OUTPUT

Sharp fall in the number of needed calculations

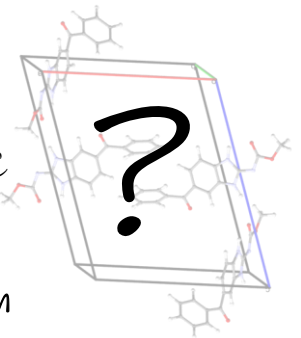
Selection of the correct crystal packing

HIGHER ACCURACY AND RELIABILITY AT LOWER COMPUTATIONAL COSTS

FOCUS OF THE WORK

MEBENDAZOLE[2]:

- 5 possible tautomers
- 3 crystal phases A, B, C
- Crystal structure of phase B **was unknown**



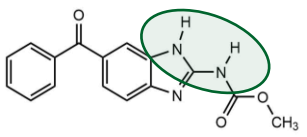
CSP-NMRX METHOD:

TEST ON PHASE A AND C
PREDICTION *DE NOVO* OF PHASE B

2D SSNMR SPECTRA: ^{13}C-^{1}H HETCOR (DOUBLE CP) and ^{1}H DQ MAS (BABA)

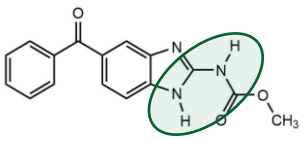
- Z'
- right tautomer assessment
- local molecular arrangement

Phase A



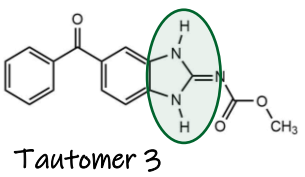
Tautomer 1

Phase C



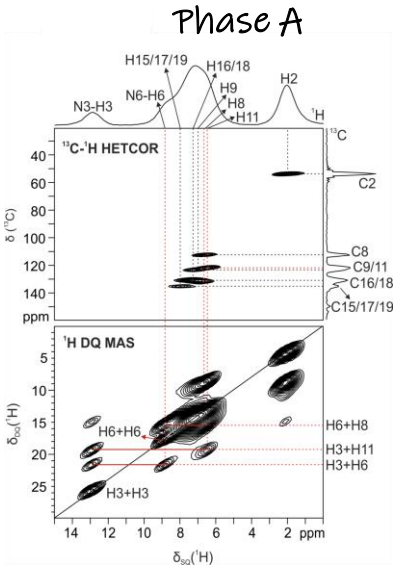
Tautomer 2

Phase B

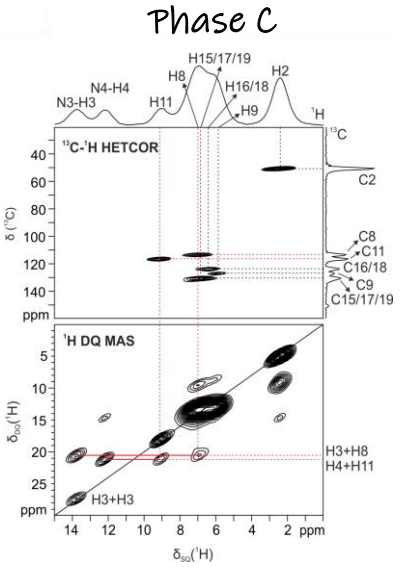


Tautomer 3

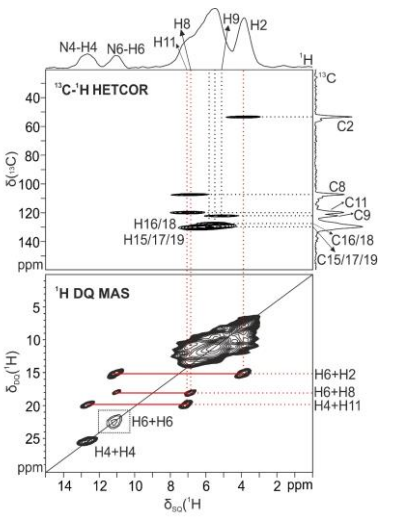
Phase A

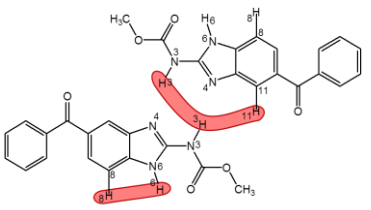


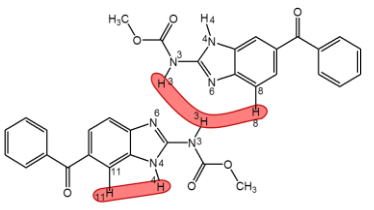
Phase C

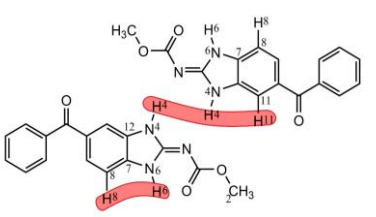


Phase B





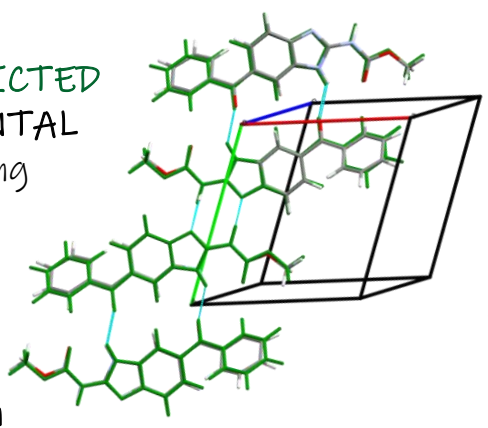


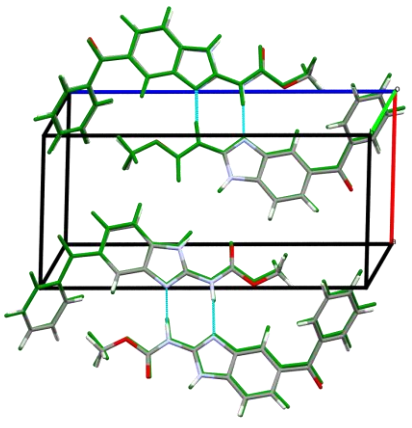


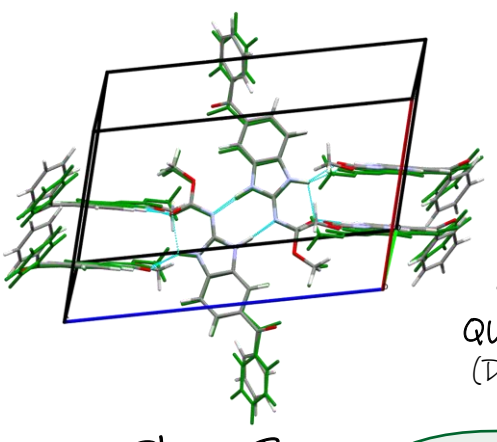
CRYSTAL STRUCTURE PREDICTION: USPEX EVOLUTIONARY ALGORITHM

Overlay of PREDICTED and EXPERIMENTAL crystal packing

Use of SSNMR for structure selection







CSP
USPEX[3] + GULP
(Dreiding FF)

Final optimization
+
SSNMR calculation
QUANTUM ESPRESSO
(DFT, PBE vdW-def2)

	Phase A			Phase C			Phase B		
	ID1	ID2	ID3	ID1	ID2	ID3	ID1	ID2	ID3
^{1}H RMSE:	0.7	0.8	1.3	0.6	1.0	0.9	0.6	0.9	0.8
^{13}C RMSE:	1.5	1.7	2.2	1.7	3.6	2.1	2.1	3.1	2.9

Structure determination *de novo* confirmed by PXRD

REFERENCES:
[1] E. Salager, G. M. Day, R. S. Stein, C. J. Pickard, B. Elena and L. Emsley, J. Am. Chem. Soc., 2010, 132, 2564–2566. [2] S. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg and G. Poochikian, Pharm. Res., 1995, 12, 945–954.
[3] A.R. Oganov, A. O. Lyakhov and M. Valle, Acc. Chem. Res., 2011, 44, 227–237; A. R. Oganov and C. W. Glass, J. Chem. Phys., 2006, 124, 244704