Improved crystal structure determination *via* utilisation of solution NMR-derived conformational information

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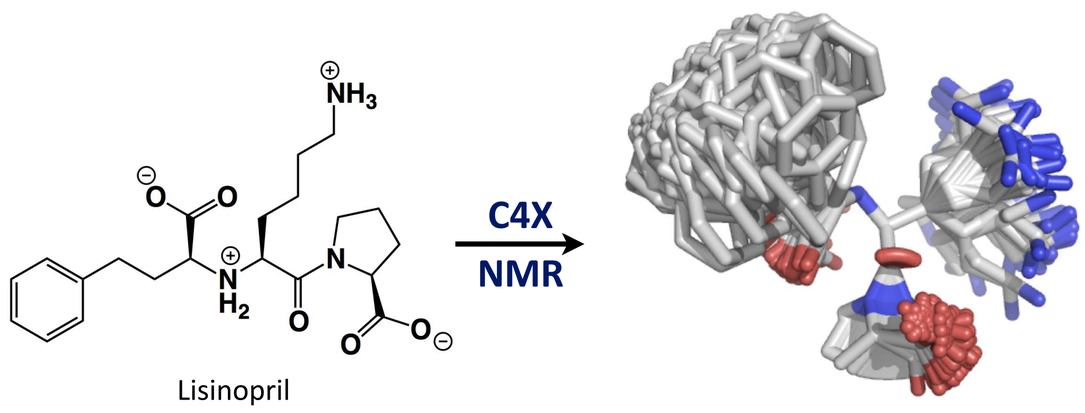
Powder X-ray diffraction

Powder X-ray diffraction is a valuable tool in the characterisation of materials and is widely implemented as an alternative to single-crystal X-ray diffraction. While crystal structure determination from powder diffraction data (SDPD) is now an established technique, it remains significantly more challenging than its single-crystal counterpart due to the relative paucity of accurate, experimentally determined structure factor magnitudes.

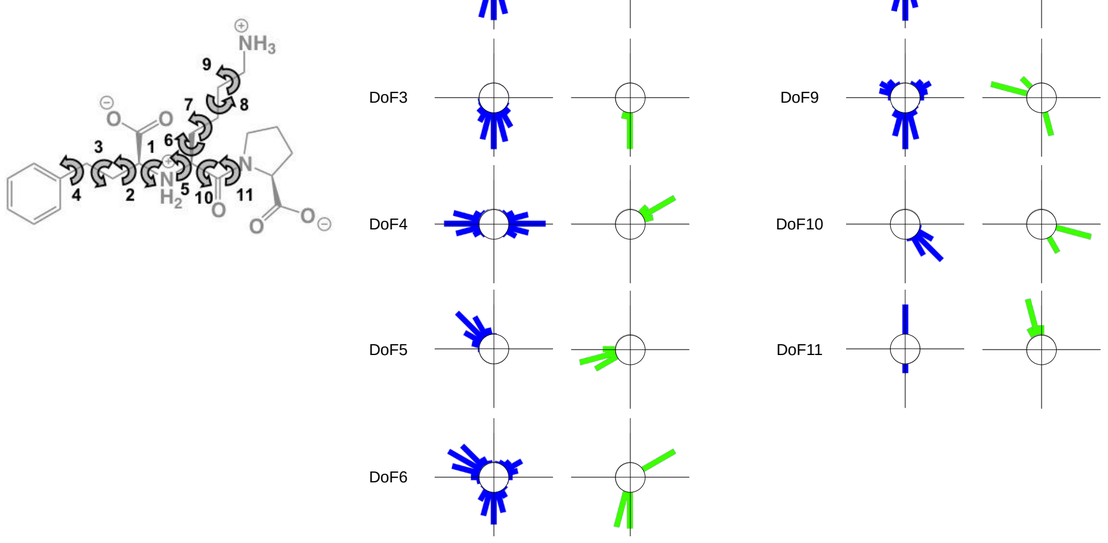
Solution NMR

Most drug molecules rapidly interconvert between a variety of conformations in free solution. C4X Discovery has developed a highly sophisticated NMR method for precisely measuring this 'conformational envelope'.[1] Importantly, the analysis can be performed in solvents directly relevant to the crystallisation conditions.



Lisinopril

Correspondence of solution and solid state conformational data



Even for quite complex drug molecules, the conformations they adopt in solution (NMR; blue) are frequently recapitulated across different crystalline forms in the solid state (green).[2] Solution NMR conformational data should therefore be an effective source of restraints for structure determination from powder diffraction data.

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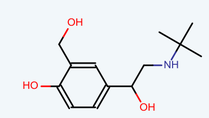
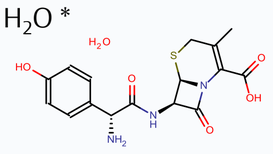
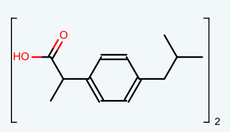
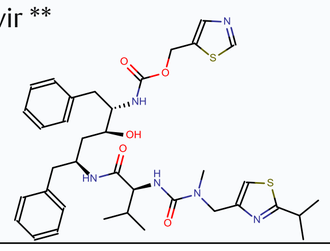
Combining the two

Global optimisation-based methods of SDPD are particularly well placed to exploit solution-NMR derived conformational information.

Such torsional information, presented as distributions, can be applied to the global optimisation-based SDPD in the form of constraints or restraints. Here, we have used the CSD-interface of the DASH structure solution program[3] to incorporate the torsional distributions.

Application

This approach has been applied to a number of pharmaceuticals of different complexity, using lab-based powder X-ray diffraction data.

Structure	DoF †	V_{cell} (Å^3)	Success rate (%) ‡ (no prior info)	Success rate (%) ‡ (with NMR info)
Salbutamol * 	11	2774.8	25	85
Cefadroxil H_2O * 	14	1786.4	0	70
Ibuprofen * (Z'=2) 	20	1248.9	0	20
Ritonavir ** 	28	3831.5	0.2	1

† Positional, orientational and torsional degrees of freedom to be determined by DASH.
‡ The % of DASH runs that reach the global minimum i.e. that solve the crystal structure.
* The reported success rates are based on 20 DASH runs of 1×10^6 simulated annealing steps.
** The reported success rate is based on 500 SA DASH runs of 5×10^7 simulated annealing steps.

Conclusions and future work

The NMR-derived torsional distributions provide valuable a-priori information that can be leveraged to enable / accelerate the SDPD of compounds of interest. It does so in a *structure specific way* which can be applied to different polymorphic and salt / hydrate forms of the structure under study. The DASH results shown above confirm the value of the approach in increasing the chances of obtaining a successful crystal structure determination, particularly with complex (large number of degrees of freedom) problems. Work is ongoing to explore the limits of its applicability and the optimal methods for inclusion of distributions.

References

1. Quantification of free ligand conformational preferences by NMR and their relationship to the bioactive conformation. Blundell CD, Packer MJ, Almond A. Bioorg Med Chem. 2013 Sep 1;21(17):4976-87
2. Measurement, Interpretation and use of free ligand solution conformations in drug discovery. Blundell CD, Nowak T, Watson MJ. Prog Med Chem. 2016;55:45-147
3. DASH: a program for crystal structure determination from powder diffraction data. David WIF, Shankland K, van de Streek J, Pidcock E, Motherwell WDS and Cole JC. *J. Appl. Cryst.* 2006;39:910-915

Acknowledgements

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