Electronic Supplementary Material (ESI) for Faraday Discussions.

Supplementary Information

Influence of Solvent on Crystal Nucleation of Risperidone

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1. PXRD results

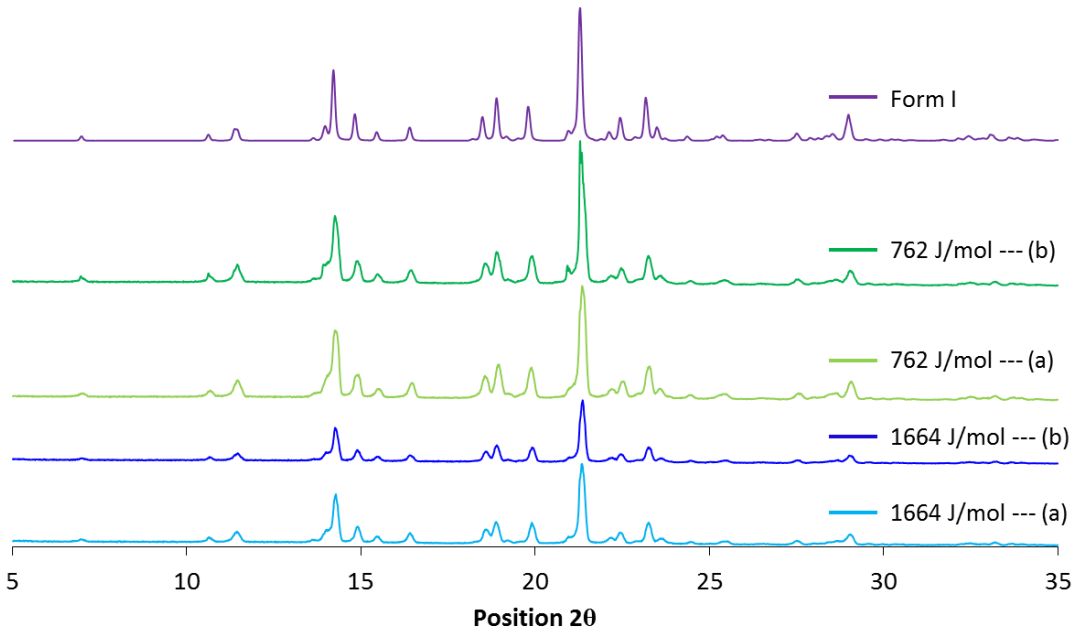


Fig. S1 PXRD patterns of risperidone solid samples of both early (a) and late (b) nucleations from toluene at both high (1664 J/mol) and low (762 J/mol) driving forces. Also shown is the PXRD pattern for pure form I for comparison.

2. Electrostatic potential maps/isosurfaces

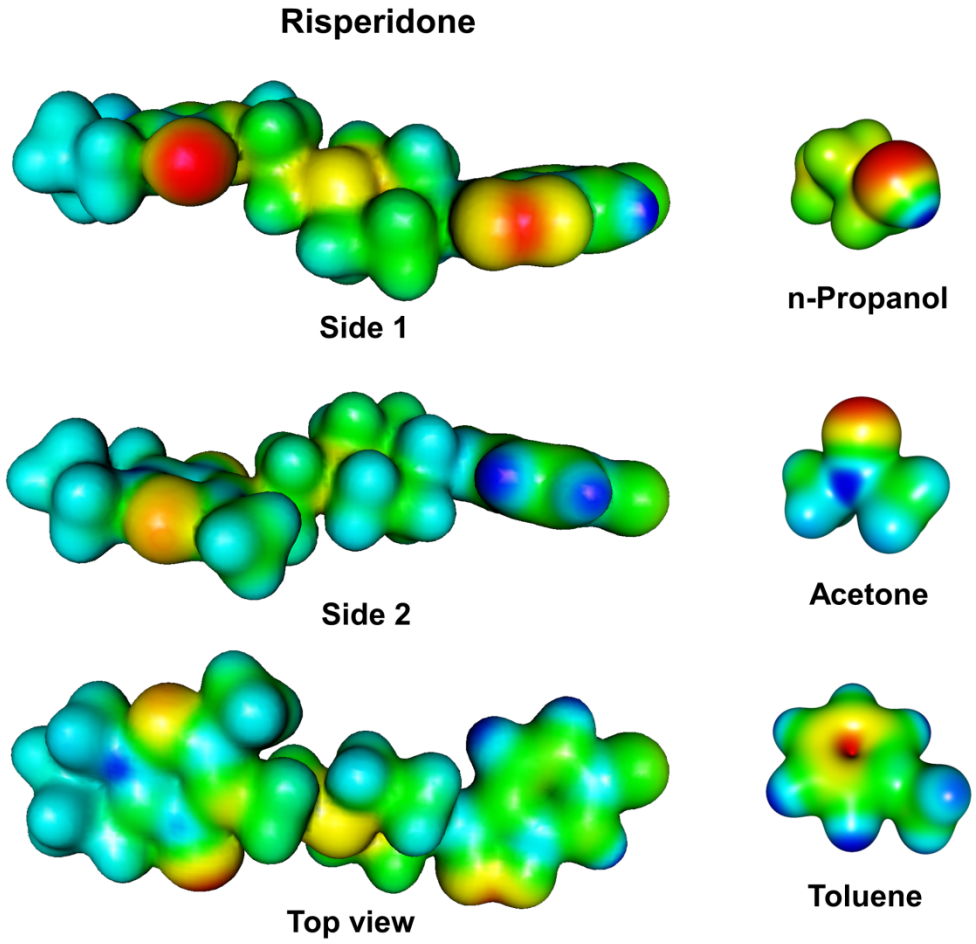
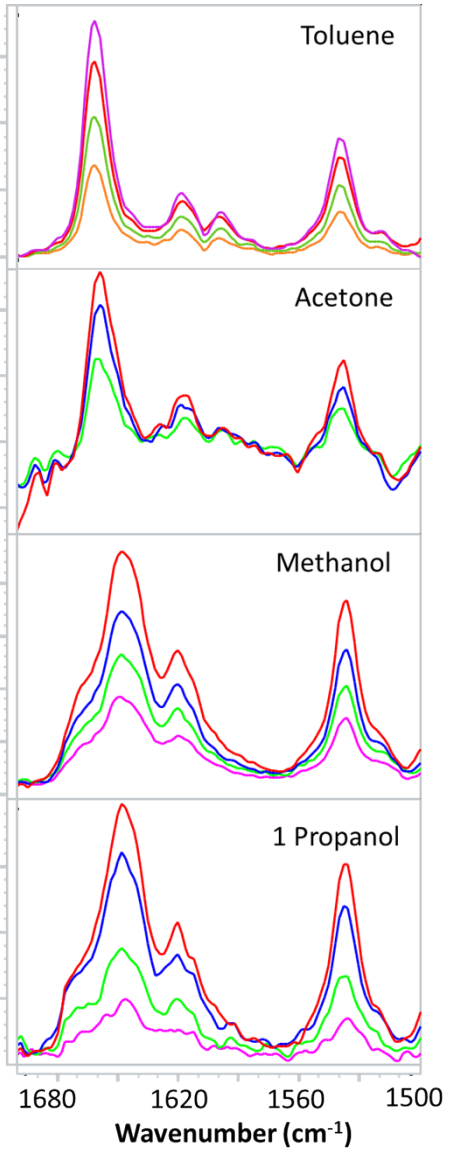


Fig. S2 Electrostatic potential maps of risperidone (three different projections) and n-propanol, acetone, and toluene (red – negative, blue – positive, and green – neutral potential).

3. FTIR data



Toluene sample	Concentration, g/l	v(C=O), cm^{-1}	v(C_4=N_3, C_1=C_2), cm^{-1}
1	23.1	1662	1540
2	18.48	1662	1540
3	13.2	1663	1540
4	8.4	1663	1540

Acetone sample	Concentration, g/l	v(C=O), cm^{-1}	v(C_4=N_3, C_1=C_2), cm^{-1}
1	7.18	1659	1538
2	5.38	1659	1538
3	3.07	1660	1538

Methanol sample	Concentration, g/l	v(C=O), cm^{-1}	v(C_4=N_3, C_1=C_2), cm^{-1}
1	36.72	1648	1536
2	26.23	1648	1536
3	18.36	1648	1536
4	12.24	1649	1536

1-Proapanol sample	Concentration, g/l	v(C=O), cm^{-1}	v(C_4=N_3, C_1=C_2), cm^{-1}
1	15.14	1648	1537
2	11.35	1648	1537
3	6.49	1648	1537
4	3.63	1647	1536

Fig. S3. IR spectra of Tolbutamide solutions at different concentrations: Toluene (8.4 to 23.1 g/l), acetone (3.07 to 7.18 g/l), methanol (12.24 to 36.72 g/l) and 1-propanol (3.12 to 13 g/l).

Wavenumber accuracy: The above figure shows the spectra after solvent subtraction. Considering solvent subtraction, the sensitivity of ATR probe and the broad nature of solution spectra, the repeated (concentration) measurement shows a good precision for wavenumbers. Since the variance in the wavenumber accuracy was less than 1 wavenumber, a respective whole integer number was used.

4. Conformational analysis

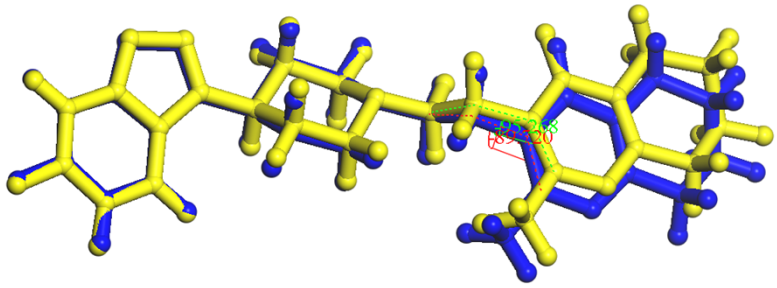


Fig. S4. The risperidone molecule in its constrained crystal lattice geometry (WASTEP) – blue, and the same molecule after optimization in isolation (DFT B97D3/6-31G(d,p)) – yellow. Highlighted is the most pronounced change of one of the dihedral angles (º).

The presence of single bonds in the risperidone molecule suggests its conformational flexibility – a common phenomenon observed in many organic molecules. It is however not fully understood to what extent the different conformations present in solution are affecting formation of a nuclei and its further rearrangement into a crystalline particle. It can be assumed that only kinetically stable conformers, so those separated by large energy barriers, could significantly affect the nucleation process. The energy barriers to rotation can be determined experimentally, e.g. via NMR spectroscopy,[1-3] or can be predicted theoretically, by employing DFT calculations.[1,2,4] The typical experimental Gibbs free energy barriers to rotation/interconversion from one isomer to another vary from few kJ mol^{-1} to more than 100 kJ mol^{-1}.[3,4] The half-life for the interconversion from boat to chair conformation in cyclohexane has been reported as 1.4 x 10^{-6} s (298K), being associated with the energy barrier of 41.8 kJ mol^{-1}.[3] Such a short half-life indicates that the barrier is too low to isolate the conformational isomers and both those conformations are kinetically unstable and easily interconverting. However, the conformational transformation is much slower if the barrier to rotation exceeds 100 kJ mol^{-1}, as it has been reported for the H-bond stabilised rotation about the C_{aryl}-N_{imide} single bond in a heterocyclic diol, where the resulting half-life for the interconversion from syn- to anti- conformation was about 27 h at 298K.[3]

The risperidone molecule consists of three rigid segments: (1) connected rings 1-2, (2) ring 3, and (3) connected rings 4-5. The segment (1) is linked by a single bond to the segment (2), which through the CH_2-CH_2 bridge is further connected to the segment (3). Altogether there are four single bonds (denoted as D1-D4 in Fig. S5) that impose flexibility to the molecule and serve as rotational centres allowing for interconversion between the different conformational isomers.

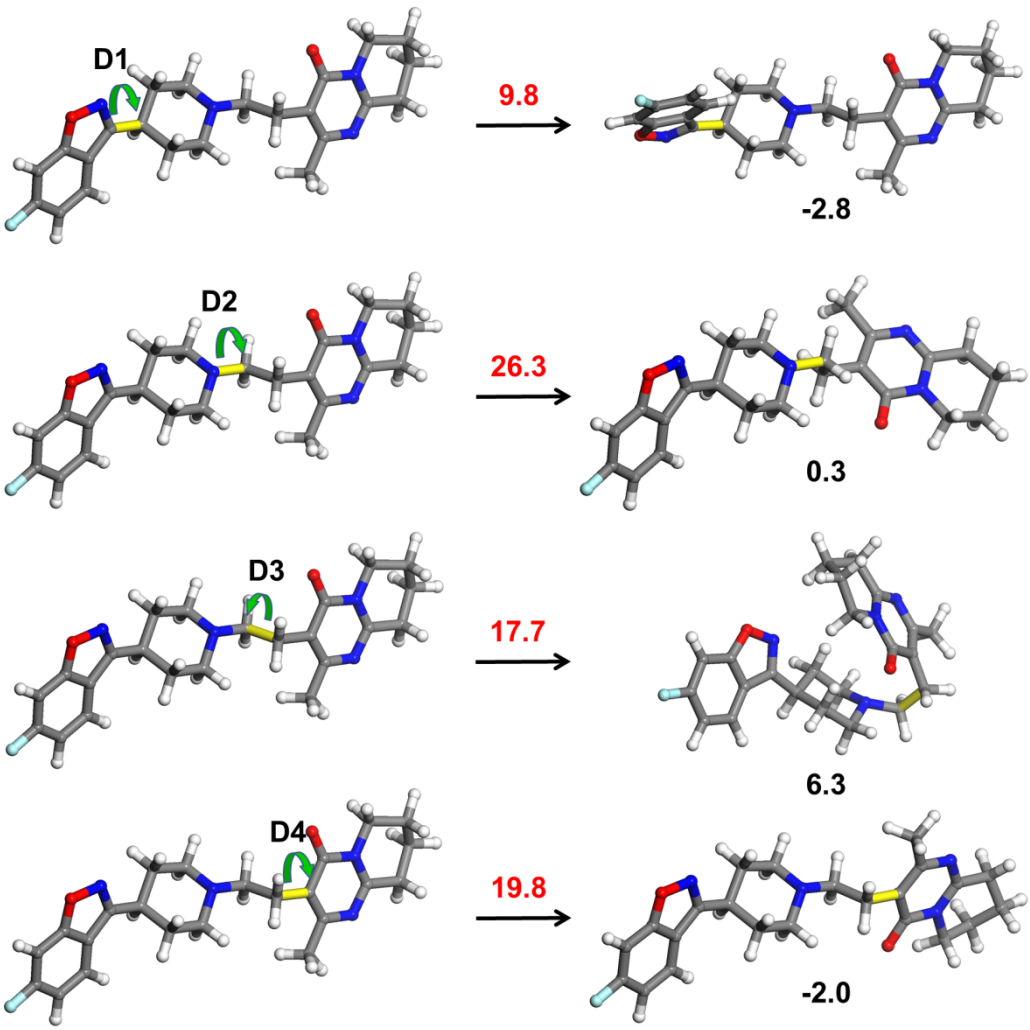


Fig. S5. Energy barriers to rotation (kJ mol^{-1}, red numbers) for four possible rotational centres D1-D4 (single bonds highlighted in yellow) of the risperidone molecule. The new low energy conformers resulting from the rotation (right column), with their relative energies (kJ mol^{-1}, black numbers) calculated as a difference between the conformer energy and the relaxed crystal lattice conformation (left column). Calculations performed at B97-D3/6-31G(d,p) (geometry) and B2PLYP-D3/def2-QZVP (energy).

By running a potential energy surface scan over the dihedral angles associated to the rotational centres, we have identified the relevant energy barriers to rotation, ranging from 10 kJ mol^{-1} to 26 kJ mol^{-1}. The relatively low energy barriers indicate high conformational flexibility of the molecule. Four new, low energy conformations had also been identified (one for a rotational centre), being structurally different from those constituting known crystal forms of risperidone. Three of them are linear, from which two conformers are slightly more stable (-2.8 kJ mol^{-1}, rotation at D1 and -2.0 kJ mol^{-1}, rotation at D4) and third (rotation at D2) is of comparable stability to the crystal-derived conformation. Rotating about the D3 centre, yields a U-shaped conformer, higher in energy by 6.3 kJ mol^{-1} as compared to the crystal-like starting conformer; this suggests the least favourable geometry (Fig. S5, Supplementary Information). The relatively small rotational barriers along with small energy differences of the three gas-phase linear conformations vs. the crystal-like conformation indicate lack

of a kinetically stable conformation that could be unambiguously chosen as a model conformation to study interactions of risperidone with solvent molecules. For this reason, the crystal-derived linear conformation of risperidone is used consistently in our modelling work.

References

1. Y. Otani, O. Nagae, Y. Naruse, S. Inagaki, M. Ohno, K et al., *J. Am. Chem. Soc.*, 2003, 125, 15191-15199.

2. X. Wang, P. A. Beckmann, C. W. Mallory, A. L. Rheingold, A. G. DiPasquale et al., *J. Org. Chem.*, 2011, 76, 5170-5176.

3. G. T. Rushton, W. G. Burns, J. M. Lavin, Y. S. Chong and P. Pellechia, *J. Chem. Edu.*, 2007, 84, 1499-1501.

4. E. Masson, *Org. Biomol. Chem.*, 2013, 11, 2859-2871.