Electronic Supplementary Material (ESI) for RSC Advances.

SUPPLEMENTAL INFORMATION

Contents:

Section S2.1. Scans of $^1J_{C–H}$ magnitudes of the azomethine (C−H) bond on N–N bond rotation.

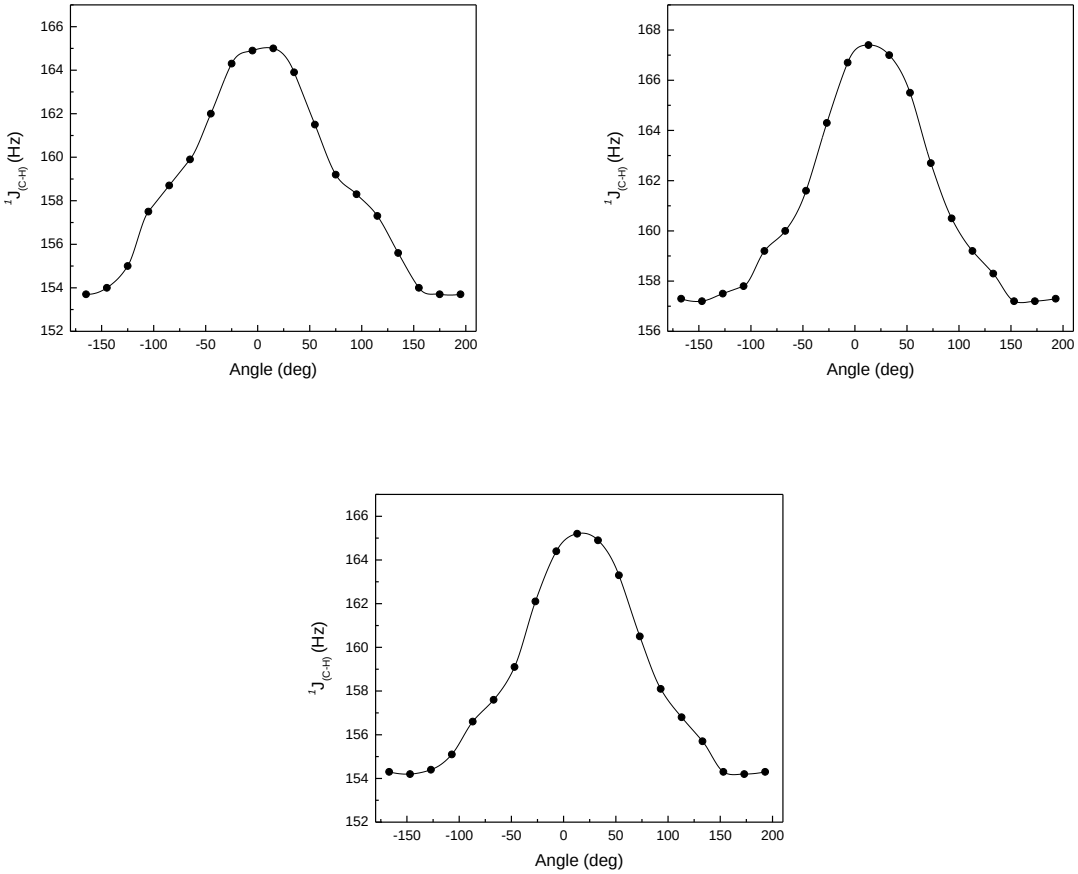


Fig. S1 Scans of $^1J_{C–H}$ magnitudes of azomethine (C−H) bond on rotation around the N–N bond for **1**, **6** and **8**, calculated using *ω*B97X-D/def2-TZVPPD approach and SMD solvent model.

Section S2.2. Effects of convergence criteria and integration grid quality

Due to the volume of calculations, many of our results have been obtained at default or, in a few cases, loose (opt=loose keyword in Gaussian) convergence criteria. Generally, even loose convergence with these systems leads to energy convergence to within < 0.01mH, which we consider sufficient for our needs.

A slightly more serious issue is grid size. A great many calculations have been done using default grid quality, which – compared to high quality grid (integral=ultrafine keyword) – does lead to errors. For energy barriers,

these errors appear to be systematic. Table S1 shows data on energy barriers from Table 8 in the main paper, recalculated at high-quality grid. In Section S2.3 we will also mention the effects on tautomerisation energies.

Table S1: Energy barriers, calculated with default and ultrafine grids.

No *o*-OH:	E_b, models ***a*** (default grid)	E_b, models ***a*H⁺** (default grid)	E_b, models ***a*** (ultrafine grid)	E_b, models ***a*H⁺** (ultrafine grid)
1	4.29	1.03	3.8	0.3
4	3.52	0.85	3.3	~0.3
5	6.22	1.32	~5.1	~0.8
With *o*-OH:				
2	3.47(4.07)	0.79(0.82)	3.1(3.6)	~0.1-0.2(~0.3)
3	3.90(4.08)	0.63(0.82)	~3.2(3.8)	~1.0(0.4)
8	3.17(3.96)	0.19(0.88)	3.1(3.7)	~<0.5(0.8)

The default grid also creates small artefacts in the energy profile on rotation around the N−N bond, with the energy maximum around *D*(CNNC) = ∼120° (the exact location varies with system) being apparently split into two peaks, as shown for the system **1*a*-H⁺$_{CO}$** (*i.e* **1*a***, protonated on CO) in fig. S2 below. This noise in the energy profile is small in comparison with the energy barrier (1.0mH, relative to *syn*). At ultrafine grid, the energy profile becomes smooth.

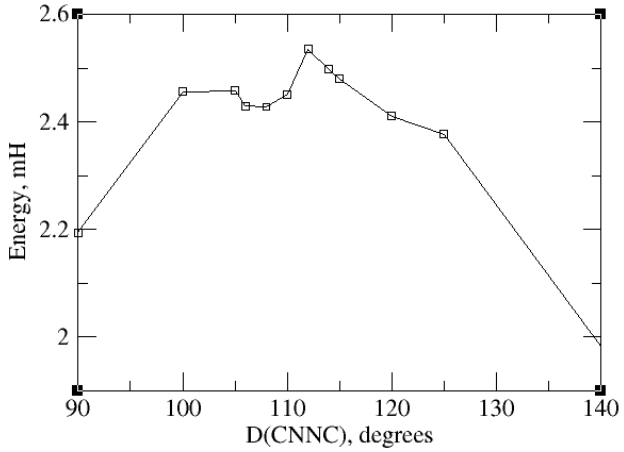


Figure S2: detail of energy profile of rotation around CNNC bond for the system **1*a*-H⁺$_{CO}$**, default grid.

Section S2.3. Variation of tautomerisation energy with external H-bonds

The tautomerisation energy of molecules **3** and **8** (with a focus on **8**) is listed below in table S1. It is defined as the difference in energies of the amine/keto and imine/enol (*syn*-conformer) tautomers (specifically, $E_{keto} - E_{enol}$). Table S2 shows tautomerisation energies for different degrees of truncation and with external H-bonds from water or C_2H_3OH to the *ortho*-O atom. We used water as an H-bond source partly for reasons of computational convenience (it being a small molecule) but also because a trace amount of water is likely to be present in DMSO solution (where it tends to accumulate over time). C_2H_3OH (ethenol) represents H-bonding by an external phenolic group, *i.e* from another quinolinone molecule. The H-bonds are to the phenolic OH involved in tautomerisation. The degree of truncation is as follows. **8*a*** is as described in the main paper. **8*i*** keeps ring C intact but removes rings A and B and truncates the heterocycle to HCO-N(R)−Me (R is -N=CH−C_6H_4OH). (**3*i*** is analogous, with R = −N=CH−C_6H_3(OH)(OMe).) **8*j*** is the full system but with ring B replaced by H. The labels U_NH and D_NH are defined in section S2.4 further down, and represent different orientations of ring B. The energies should be taken as approximate, with the qualification that it is difficult to exhaustively sample the full potential energy surface with a solvent molecule attached (*i.e* with respect to all the possible orientations of the solvent molecule). Furthermore, as mentioned in the main paper, the two tautomers have different *D*(CNNC) values, and the relative energy of the keto form at the *D*(CNNC) value of the *syn*-enol is about 1.5-2mH higher than the energies given below. Proper treatment of this subject would require molecular dynamics.

Table S2: Tautomerisation energies ($E_{keto} - E_{enol}$, in mH) for systems **3** and **8**, both full molecules and truncated, with external H-bonds to hydroxyl oxygen (ring C) from listed molecules. Default grid was used for all calculations, except those in **bold**, which used an ultrafine grid for comparison.

Solv. molecules:	**8**, full (U_NH)	**8**, full (U_NH), ultrafine grid	**8**, full (D_NH)	***8a***	***8a***, ultrafine grid	***8i***	***8j***	***3i***	**3**, full (D_NH)
none	9.9	**10.1**	10.7	11.3	**9.2**	9.6	9.9	10.0	11.1
$+H_2O$	8.3	**7.5**	8.1	4.4	**4.5**	4.8	4.9	5.3	--
$+2H_2O$	0.0	**--**	--	1.5	**1.4**	2.3	0.7	3.1	--
$+C_2H_3OH$	2.2	***3.9***	3.8	4.3	**1.7**	--	2.4	3.0	8.8
$\{+C_2H_3OH +H_2O\}$				*-0.4*					

The various degrees of truncation listed above make little difference to the tautomerisation energies of the lone molecule; however, some smaller systems with ring C truncated show *negative* tautomerisation energies, *i.e* the keto form is *lower* in energy than the enol form. One such is discussed in the next section; another is the near-minimal system HCO−N(Me)−N=CH−CH=CH−OH. Overall, the picture is fairly clear: any H-bonds to the phenolic oxygen on ring C stabilise the keto tautomer, with H-bonds from ethenol having a stronger effect than water. We thus consider it plausible that external H-bonds catalyse the reversion of the *syn*- to the *anti*-conformers by way of the keto form as an intermediate, when *o*-OH groups are present. We must note, however, that preliminary calculations on another system with *o*-OH, molecule **3**, find slightly less of an effect from external H-bonding, with full **3** having quite a high tautomerisation energy even with ethenol. For completeness, we also calculated ***8a*** (no solvent) *in vacuo* (i.e. with no SCRF): the tautomerisation energy was +17.7mH, as compared to +11.3mH using SCRF to simulate a DMSO environment.

We further note that these numbers may be *very* sensitive to the level of the calculations. This has not been extensively checked, but as an example: for the full (D_NH) system **8** + H_2O, the tautomerisation energy for our standard basis (6-311G++(2d,2p)) is 8.14mH, as listed above. If the basis set is reduced to 6-31G+, this value decreases to 1.55mH! Thus we have a situation where a desired property (tautomerisation energy) is highly sensitive to basis set, fairly sensitive to model size, and probably very sensitive to solvent molecule orientation and dynamics. It would be nice to calibrate our calculations to post-HF calculations, but a large part of what needs calibrating is the treatment of the large extended π-system, which is simply not feasible at post-HF level.

Section S2.4. Commentary on isomers caused by ring-B H-bonding.

Our systems have conformational freedom with regards to the orientation of ring B. This is potentially important when both rings B and C have *o*-OH, as the ring B *o*-OH could conceivably interact with the heterocycle and the N-N=C moiety. To examine this, several calculations have been done on a system we will label ***8k***: this is system **8** with ring A removed and ring C truncated to N-N=CH-CH=CH-OH. This system is shown below. Some calculations have also been done on the full system.

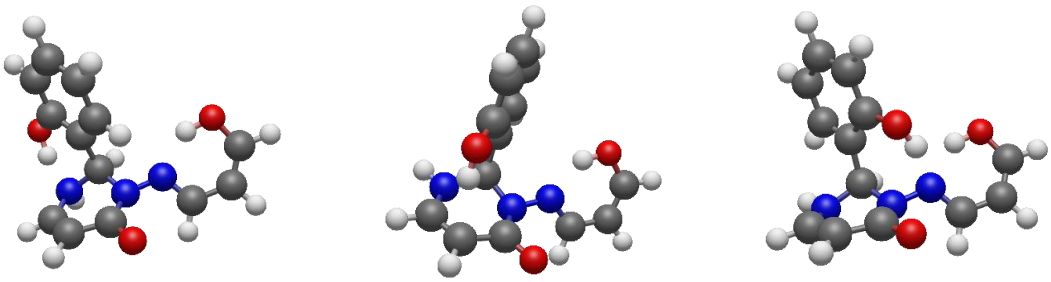


Figure S3: conformers of ***8k*** eD_NH, eD_CH, eD_NN. Conformers eU_NH, eU_CH and eU_NN are similar but with the OH bond on ring C pointing up.

The labelling for the multiple conformers of Ring B is as follows. (In all cases we shall examine the *syn* conformer.)

Position of OH above the heterocycle: **NH** indicates that the ring B OH group is interacting with (H-bonded to, or located above) heterocycle-NH (atom label "1" in Fig. 1 in the main paper); **CH** indicates it is interacting with the CH=**C**H−CO carbon (atom label "4a"), and **NN** indicates interaction with N−**N**=C nitrogen (atom label "9"). We also attempted to set up interaction with the C=O group (labeled **CO**), though in our calculations this was not found to be a local minimum and the H-bond migrated to the **NN** or **CH** positions.

Orientation of O-H bond: **D** and **U** mean "down" and "up", according to whether the OH group is pointing "down" at the rest of the molecule (*i.e* H-bonded) or not ("up").

Protonation states: the imine/**e**nol tautomer is labelled **e**; the amine/**k**eto tautomer of the truncated ring C is **k**; and **q** is the not-**q**uite-tautomer caused by ring B hydroxyl donating a proton to whatever it is interacting with. The sequence of these labels will be {**e/k/q**}{**U/D**}_{**NH/NN/CH/CO**}. Energies relative to eU_NH are shown in table S3 below, for both **8*k*** and the full molecule **8**.

Table S3: Relative energies (in mH) of various different conformers/tautomers of truncated and full version of molecule 8, given relative to eU_NH. See text for explanation of labels. [a)] For **q**, there are no **U** and **D** forms, as these refer to the orientation of hydroxyl proton, which in the **q** form has been transferred elsewhither. [b)] For qD_NN, *A* and *B* have different orientations of the phenolate O on ring B.

Ring B position:	Truncated system (**8*k***)			Full molecule **8**
	e (enol)	**k** (keto)	**q** (quito)[a]	**e** (enol)
D_NH	3.3	-5.9	*Optimizes to eD_NH*	-0.7
D_CH	1.3	-8.6	--	5.4
D_CO	*Optimizes to eD_NN*	*Optimizes to kD_CH*	*Optimizes to eD_NN*	--
D_NN	5.5	1.9	*A*: ~15[b]	4.1
			B: ~26[b]	
U_NH	0.0	-9.5	--	0.0
U_CH	4.6	-6.6	--	3.1
U_NN	3.0	--	--	6.0

It is important to note that the tautomerisation energies are *negative* for the truncated system (whereas – see previous section – these energies are positive for larger models and the full system); and the relative energies of the various ring B conformers are different for the full and the truncated molecules. Thus, the truncated molecules are not completely reliable as a guide to the behaviour of the full system. However, the energy for internal proton transfer from ring B (**q** vs. **e**) is higher than the tautomerisation energy either of **8*x*** or of any of the systems listed in the previous section. Provisionally, then, we think that tautomerisation takes place to a higher degree than internal proton transfer from ring B. (Of course, it is likely that solvent interactions and H-bonds to deprotonated ring B will mitigate the protonation energies.)

In both cases, truncated and full molecule, it can be seen that internal H-bonding from the OH on ring B is weak. For the enol, the form with an internal H-bond is higher in energy in many cases (truncated enol: NN, NH; full enol: CH); and where the internal H-bond does lower the energy, the energy difference is small – at most 2.5mH (truncated enol, eU_CH vs. eD_CH). The numbers are similar for truncated enol and truncated keto. Note that in solution, the **U** forms would be stabilised over the **D** forms due to H-bonding to solvent (see section S2.5, where we estimate the H-bond strength as >13mH, far stronger than the weak internal H-bonds discussed above) so we expect the **U** forms to predominate.

In addition, there are diastereomers in which Ar (ring B) and H are swapped on the **C**H-Ar_B carbon (atom number 2), *i.e* we can have an isomer where ring B points out sideways from the heterocycle instead of perpendicularly. This is illustrated in Figure S4. Our calculations on **8*k*** indicate that, for eD_CH, the transition to this isomer is energetically favourable, with the internal H-bond shifting from OH···C=C to OH··N and the energy barrier being small. However, conversion to this diastereomer would inhibit relaxation to the *anti*-conformer (ring B would be in the way of the N=CH moiety); and experimentally we *do* see relaxation to the *anti*-conformer, so we must conclude that conversion between diastereomers does not happen for the real system, probably due to conformer eD_CH being unavailable for reasons already discussed (**U** conformations being favoured due to H-bonds to solvent becoming possible).

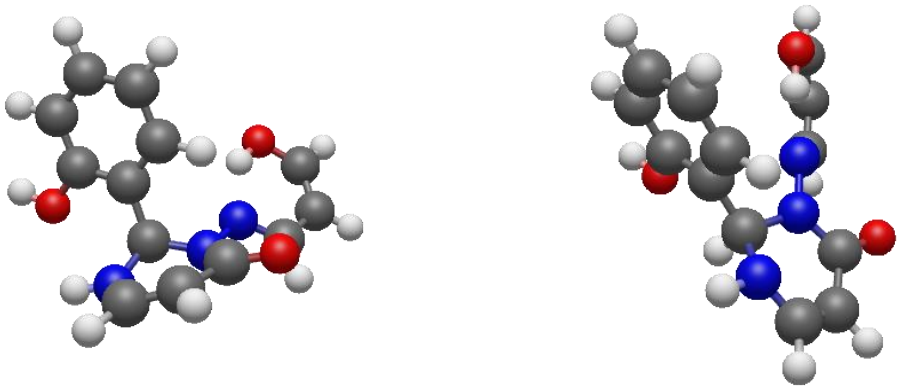


Figure S4: diastereomers of **8*k*** with ring B perpendicular to (left; eU_NH) and sideways from (right) the heterocycle.

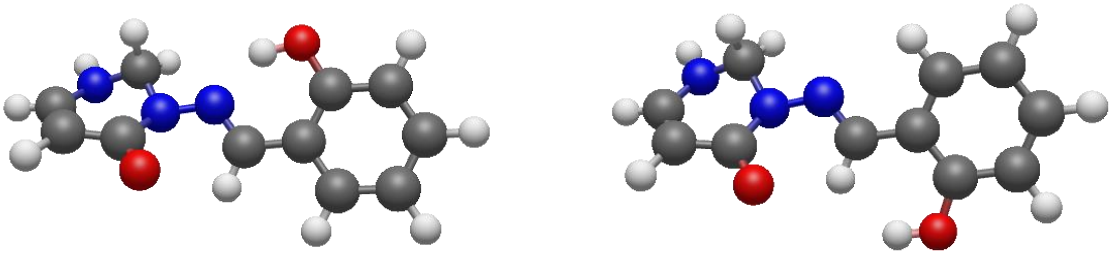
For eD_NN and eD_NH, the transition to the other diastereomer is unfavourable as it proceeds to a conformer with no internal H-bond. However, the resulting diastereomer would presumably H-bond to solvent molecules, stabilising it.

Proper examination of the energies of the diastereomers would need inclusion of solvent molecules. It would be interesting as it would tell us whether the diastereomer seen in experiment and treated by our calculations is only a local minimum, and hence whether the *anti*-conformer is thermodynamically or only kinetically stable. However, this must remain a topic for possible future work.

Section S2.5. Rotation around C-Ar bond (ring C).

This subsection will assume the molecules are in *syn* conformation across the C(O)−N−N=C linkage and will only look at rotation around the C-Ar bond, which we have labelled *(syn)* vs. *(anti)*. For system **1*a***, *i.e* with R = Ph, the barrier to rotation around the C-Ar bond for ring C is estimated at 8.4mH.

For system **8*a***, *i.e* with R = *o*-hydroxyphenyl, there is the complication that the hydroxyl H can point towards (**A**), or away from (**B**), the rest of the molecule, and this interacts with whether the OH group is *(syn)* or *(anti)* relative to the C=N moiety. (**A**)*(syn)* has an internal H-bond, and is thus more stable (by >9mH) than the other conformers. (**B**)*(anti)* has a weak internal H-bond interaction between azomethine H and hydroxy O. The other two forms are expected to be less stable: (**A**)*(anti)* has steric repulsion between the hydrogens of the OH and N=CH groups, and (**B**)*(syn)* has repulsion between the lone pairs of two electronegative atoms, imine N and hydroxy O. For comparison, calculations on the full compound **8** showing (**A**)*(syn)* to be 11.7mH lower than (**B**)*(anti)*. The conformers are shown in Fig. S5 below.



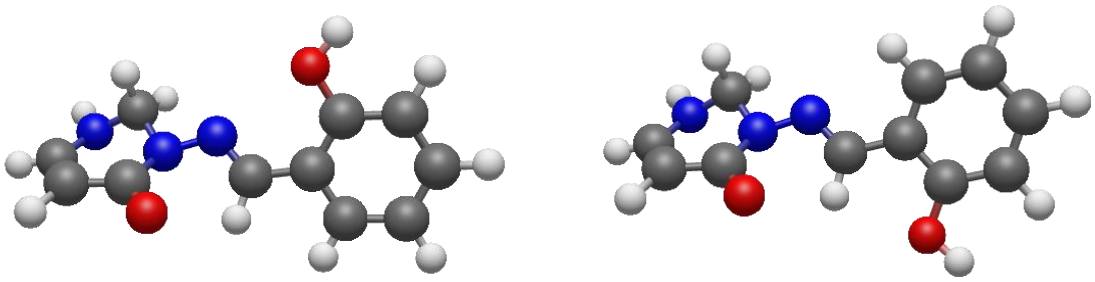


Figure S5: various conformers of **8*a***. Top: (**A**) conformers (hydroxyl H pointing towards N-N moiety). Top left: (**A**)*(syn)*. Top right: (**A**)*(anti)*. Bottom: (**B**) conformers (hydroxyl H pointing away from N-N moiety). Bottom left: (**B**)*(syn)*. Bottom right: (**B**)*(anti)*.

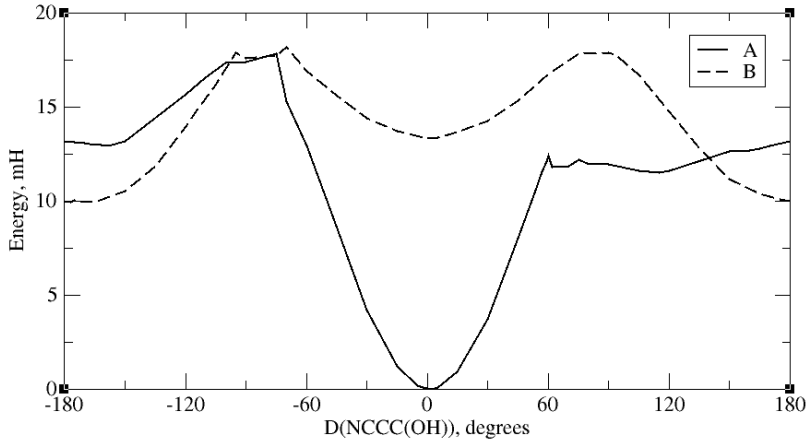


Figure S6: Energy profile (mH) of **8*a*** on rotation around the C-Ar_C bond for **(A)** and **(B)**.

As seen in fig. S6, (**A**)(*syn*) is most stable, with (**A**)(*anti*) forming a very shallow energy minimum due to steric repulsion between hydrogens. From this, one would expect (**A**)(*syn*) to predominate in solution. However, these data ignore the possibility of the hydroxyl group H-bonding to solvent molecules. This would remove or reduce the energy advantage of the (**A**)(*syn*) conformer, as the H-bond with solvent is likely to stabilize the other forms by >13mH.

(Regarding which: we calculated the H-bond strength of phenol to DMSO as 13.7, and of *ortho*-hydroxyphenylmethylimine (HN=CH−C_6H_4−OH) to DMSO as 14.6mH, at ωB91XD//6-311G++(2d,2p) with SMD(DMSO). BSSE calculations for phenol + DMSO (without SCRF) indicate that BSSE leads to an overestimate of H-bond strength of 0.5mH; BSSE+SCRF calculations are not available in Gaussian, but we doubt that BSSE is significantly affected by SCRF. Thus, we estimate H-bond strengths to DMSO as ∼13mH for phenol and ∼14mH for HN=CH-C_6H_4-OH.)

Therefore, calculations were done on (**A**)*(syn)* to (**A**)*(anti)* rotation with the initial system having a forked H-bond to both N9 and a DMSO molecule, and then for (**A**)*(anti)* to (**B**)*(anti)* – see Fig. S7 below for a depiction of the system.

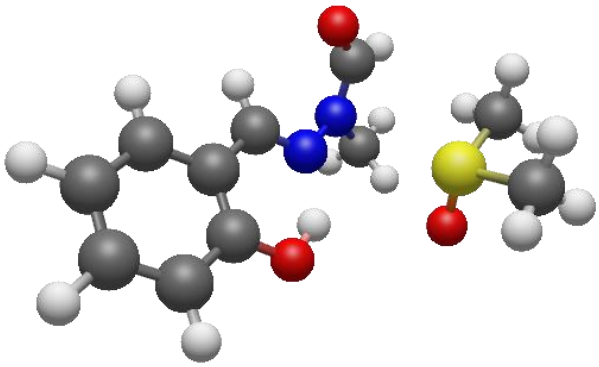


Figure S7: molecule **8*a***, in (**A**)(*syn*) form, with the hydroxyl proton interacting with (forming a forked H-bond to) both imine-N (N9) and DMSO.

On doing this, we find that (**A**)*(syn)* is still lowest in energy, but (**A**)*(anti)* is only 0.4mH above it, and (**B**)*(anti)* 0.4mH higher still. Thus (**A**)*(anti)* is significantly stabilised, with the steric repulsion between hydroxy H and azomethine H being counteracted by the fact that both hydrogens can engage in H-bonding interactions with the solvent (see fig. S7 above.) Thus from a thermodynamic point of view, if these calculations are correct, we estimate that the equilibrium should be ~20% (**B**)*(anti),* ~30% (**A**)*(anti)* and ~50% (**A**)*(syn)*. However, the energy barrier of rotation from (**A**)*(syn)* to (**A**)*(anti)* is still fairly high, though reduced from >12mH to ~7.5mH by solvent interaction; it is possible that this equilibrium is reached too slowly to be observed. In fact, we do not see any indication of equilibrium between these forms in our experiments, so we presume that only one of them is present. As mentioned in the main paper, we assume this is (**A**)*(syn)*, as this fits NMR data better (although not conclusively so) and as it would give us an explanation (tautomerisation and/or internal H-bonding + protonation) for why *o*-OH groups speed up *syn-anti* relaxation; but we are far from certain.

These calculations are not definitive: they involve a forked H-bond turning into a simple H-bond, whereas in fact a second solvent molecule could also move in to replace the OH···N_{imine} interaction. However, test calculations on the formation of (**B**)*(anti)* with forked H-bonds to two DMSO molecules give *E*[(**B**)*(anti)* + 2DMSO] – *E*[(**A**)*(syn)* + DMSO] – *E*[DMSO] ~ +9mH, similar to estimates with only one DMSO, and sufficiently positive that it is unlikely to happen. (No BSSE correction has been applied, but we assume that the BSSE is of similar size to that of phenol-DMSO, *i.e* <1mH.) Such situations, involving interactions with multiple solvent molecules, really call for the use of molecular dynamics for proper treatment; but that is beyond the scope of this Supplemental Information.

Section S2.6. Protonation energies for small models.

Table S4: Protonation energies (in mH) of model set ***a*** for protonation of N9 and CO. For systems with *o*-OH, conformers *syn*(*syn*) are given outside of brackets, while values for *syn*(*anti*) are given in brackets.

No *o*-OH:	E_{prot} (N9)	E_{prot} (CO)
1	-436	-433
4	-441	-434
5		-429
With *o*-OH:		
2	(-439)	-431(-433)
3	(-439)	-430(-433)
8	-443(-439)	-439(-433)