Electronic Supplementary Material (ESI) for Chemical Communications

Controlling Molecular Tautomerism Through Supramolecular Selectivity

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1. Computational

VASP geometry optimizations

Geometry optimizations of crystal structures were performed using the program VASP.[1] The functional PBE[2] with PAW pseudo potentials[3] were used with Grimme's van der Waals corrections[4] and a kinetic energy cut-off for the plane-waves of 520 eV. The Brillouin zone was sampled using the Monkhorst-Pack approximation[5] and a grid of k-points separated by 0.07 Å. Structural relaxation was stopped when the calculated force on every atom of the cell was less of 0.001 eV/Å.

Gas-phase energies of the tautomers, as presented on Figure 1 of the manuscript, were calculated by geometry optimizing the individual tautomers with VASP using fixed supercells of 20 x 20 x 20 Å using the parameters above.

Tautomer Energies

The relative stability of tautomers 3H and 1H of 1-deazapurine were calculated with various computational methods and are summarized in table S1. Gas-phase geometry optimizations of the isolated tautomers were performed using GAUSSIAN09[6] at different level of theories. B97d, MP2 and CCD calculations with cc-pVTZ basis set seem to agree within 3.6 kJ/mol. The use of augmented basiss set (aug-cc-pVTZ) did not seem to considerably influence the tautomers relative stabilities. Higher order methods (CCD) predict slightly larger tautomeric energy differences in the gas-phase. After the gas-phase geometry optimizations, single point energy calculations with a Polarizable Continuum Model (PCM), using the Tomasi and coworkers approximation,[7] were performed using the optimized geometries for each level of theory. Two calculations were performed per each geometry: a) a single point energy calculation with a PCM model with an effective dielectric constant of $\varepsilon = 3$, typical of organic crystals,[8] and b) a single point energy calculation with an acetone PCM model, (acetone is the solvent later used in experimentation). All models and all levels of calculations predict the 3H tautomer being the most stable. As we go from a gas-phase environment to a more polarizable medium like acetone, however, the tautomers relative stabilities shrink considerably. In some tautomeric compounds, the relative stability of tautomers has been reported to even invert in different media.[9] The relative stability of the 3H and 1H tautomers in a crystal environment is somewhere in the middle between the isolated molecule approximation (gas-phase) and a polar solvent (acetone).

Isolated tautomers were also optimized using periodic boundary conditions with VASP as detailed in the section above. VASP calculations are in good agreement with the isolated molecule GAUSSIAN09 calculations in the gas-phase (Table S1).

Table S1. Relative energies for the 3H and 1H tautomers of 1-deazapurine in the gas-phase.

Tautomers Relative energies (kJ/mol)						
	Gas-phase		PCM Crystal Environment (ε = 3)		PCM Acetone Solvent	
	3H	1H	3H	1H	3H	1H
PBE-D2/PAW 520eV[b]	0.0	14.8	-	-	-	-
B97d/cc-pVTZ	0.0	15.4	0.0	8.7	0.0	2.4
B97d/aug-cc-pVTZ	0.0	15.1	0.0	8.3	0.0	1.6
MP2/cc-pVTZ	0.0	18.5	0.0	10.8	0.0	3.5
MP2/aug-cc-pVTZ	0.0	18.0	0.0	10.3	0.0	3.0
CCD/cc-pVTZ	0.0	19.0	0.0	11.3	0.0	4.2
CCD/aug-cc-pVTZ*	0.0	18.0	0.0	10.8	0.0	3.6

* Single point energy calculation only from the CCD/cc-pVTZ optimized geometry.

Crystal Structure Prediction

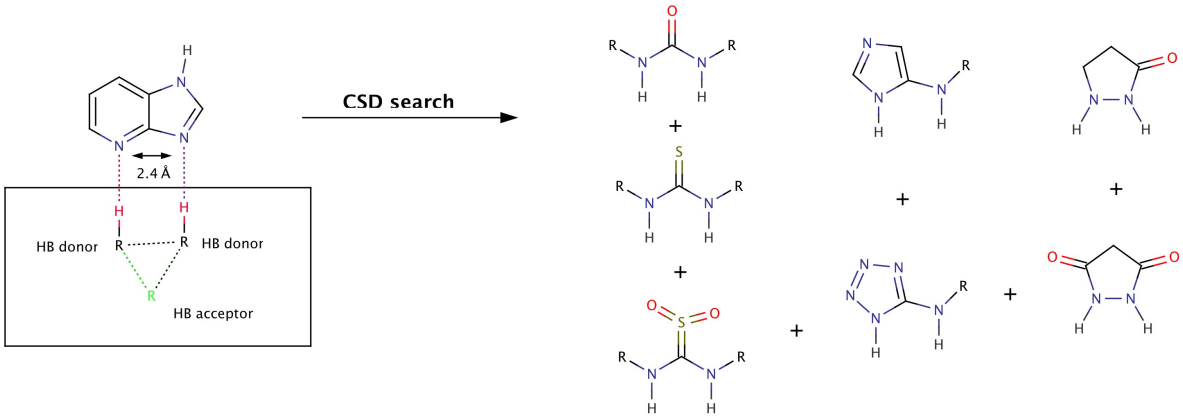
Z'=1 crystal structures were generated for the 3H and 1H tautomers using the software CrystalPredictor.[10] Two independent searches were performed (1 per tautomer) in 18 of the most common space groups. Space groups searched included: $P1$, $P\bar{1}$, $P2_1$, $P2_1/c$, $P2_12_12$, $P2_12_12_1$, $Pna2_1$, $Pca2_1$, $Pbca$, $Pbcn$, $C2/c$, Cc, $C2$, Pc, $P2_1/m$, $C2/m$, $P2/c$, $Pccn$, $Pnma$, $R3$ and $R\bar{3}$. 200'000 structure minimizations were performed per independent crystal structure prediction search. The molecular models used at the beginning of the search were taken from the gas-phase geometry optimized molecules at the MP2/cc-pVTZ level of theory using GAUSSIAN09. The tautomer models were kept rigid during the search and first optimization procedure. Atomic charges were derived to fit the molecule electrostatic potential (ESP charges).

The Williams 99 forcefield[11] was used for the evaluation of the van der Waals interactions using a cut-off of 15 Å and the ESP charges were used for the evaluation of the electrostatic interactions which were evaluated using the Ewald summation method. The 50 most stable crystal structures generated for each tautomer were then re-optimized with VASP.

Topological Search for Possible Coformers

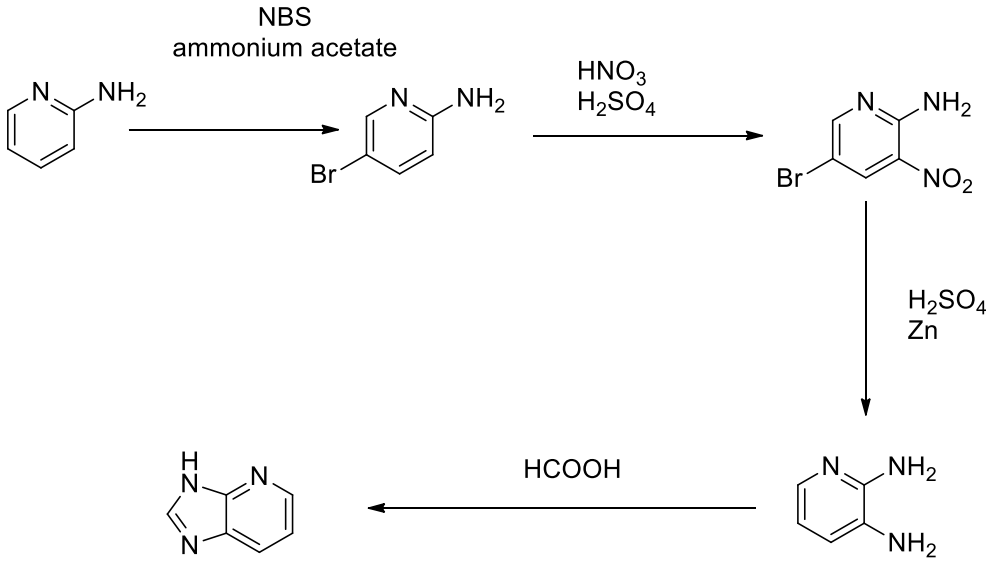
For the design cocrystals of the 1H-tautomer, we needed a co-crystallizing agent capable of forming two coplanar hydrogen bonds (both as donors) separated by a distance of ~2.4 Å (the distance between the imidazole and the pyridine basic nitrogen atoms in the 1H tautomer) with an accessible hydrogen-bond acceptor at the opposite end of the molecule (Figure 2, right). A search of the Cambridge Structural Database[12] for such molecular topology resulted in several

possible candidates including urea and thiourea derivatives or amino-pyrazoles. See figure below.

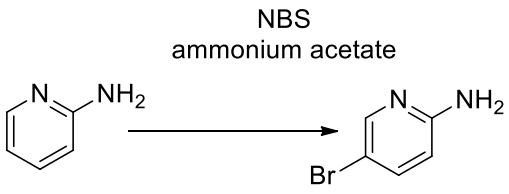


2. Experimental

Synthesis



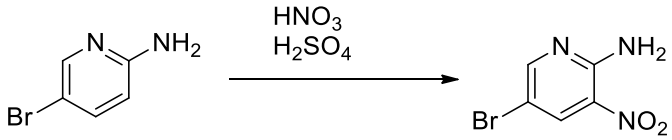
Synthesis of 2-amino-5-bromopyridine



2-Aminopyridine (5 g, 53 mmol) was dissolved in 150 ml of acetonitrile. 20 g of ammonium acetate was added to it. NBS (9.9g, 53 mmol) was slowly added to the stirring suspension dropwise. The absence of starting material was confirmed via TLC in about 15 minutes. The acetonitrile was removed under reduced pressure. The solid was dissolved in ethyl acetate,

washed with water and brine and dried over $MgSO_4$. Ethyl acetate was removed under reduced pressure yielding a light brown crystalline solid. (8.2 g, 90%) m.p. 115-120 ^{0}C, ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.42 (1 H, d, *J*=8.98 Hz), 7.50 (1 H, dd, *J*=8.59, 2.34 Hz), 8.11 (1 H, d, *J*=2.34 Hz)

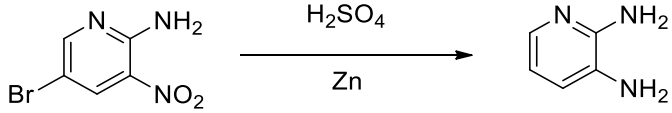
Synthesis of 2-amino-3-nitro-5-bromopyridine



2-aminopyridine-5-bromopyridine (2 g, 11.6 mmol) was carefully dissolved in 30 ml of H_2SO_4. The mixture was cooled to 0 ^{0}C. HNO_3 (0.8 ml, 11.6 mmol) was added dropwise to the stirring solution. The solution was stirred at 0 ^{0}C for two hours and heated to 50 ^{0}C for another two hours. The yellow liquid was poured on to 10 g of crushed ice and the yellow precipitate was filtered out. (2.25 g, 88.9%) m.p. 192-198 ^{0}C

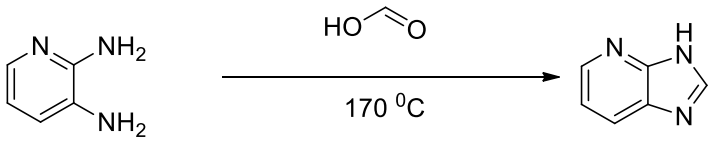
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.07 (2 H, s), 8.49 (1 H, d, *J*=2.34 Hz), 8.52 (1 H, d, *J*=2.34 Hz)

Synthesis of 2,3-diaminopyridine



2-amino-3-nitro-5-bromopyridine(0.5 g, 2.30 mmol) and Zn dust(0.83g, 12.6 mmol) were added to 8 ml of water and 5 ml of methanol. Conc. H_2SO_4 (0.733 ml 13.76 mmol) was added to the suspension and heated at 90^0 C for 48 hours. The absence of reactants was confirmed by TLC. An excess of Na_2CO_3 was added to the suspension and any solvent present was removed under reduced pressure. The product was extracted to methanol. The methanol was removed under reduced pressure and the solid obtained was extracted with ethyl acetate. The ethyl acetate was dried over $MgSO_4$ and removed under reduced pressure to obtain the product (0.05 g, 20%). m.p. 92-95 ^{0}C ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.61 (2 H, br. s.), 5.29 (2 H, br. s.), 6.36 (1 H, d, *J*=4.69 Hz), 6.67 (1 H, d, *J*=7.42 Hz), 7.26 (1 H, d, *J*=5.08 Hz)

Synthesis of 1-deazapurine



2,3-diaminopyridine (1.0 g, 9.16 mmol) was mixed with formic acid (0.5 ml, 13.2 mmol). The resulting mixture was heated at 170 ^{0}C for 48 hours. The excess formic acid was removed under reduced pressure and the remaining solid was dissolved in 100 ml water. The product was extracted to ethyl acetate 100 ml X 4. The ethyl acetate was removed under reduced pressure to yield the pure product. (0.33g, 30%) m.p. 125-130 ^{0}C 1H NMR (400 MHz, DMSO-d6) d ppm 7.23 (1 H, dd, J=7.81, 4.69 Hz), 8.02 (1 H, d, J=7.81 Hz), 8.35 (1 H, d, J=4.90 Hz), 8.43 (1 H, s), 12.91 (1 H, br. s.)

Synthesis of diphenylurea U1

Phenylisocyanate (2.14 ml, 19.5 mmol) was dissolved in 10 ml of hexane. Aniline (1.82 ml, 19.7 mmol) was added to the above solution dropwise very slowly. The mixture was stirred for one hour. The white precipitate was filtered out. (3.90 g, 95%) m.p. 235-239 ^{0}C ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.92 - 7.01 (2 H, m), 7.22 - 7.31 (4 H, m), 7.44 (4 H, d, *J*=8.59 Hz), 8.66 (2 H, s)

Synthesis of 1-(2-Cyanophenyl)-3-phenylurea U3

Phenyl isocyanate (0.7 mL, 6.3 mmol) was dissolved in CH_2Cl_2 (20 mL) at room temperature and 2-amino benzonitrile (0.75 g, 6.3 mmol) was added in one portion. After 5 min a white solid began to settle out. After stirring for 4 - 5 days, the white precipitate was filtered and washed with cold CH_2Cl_2 and dried under vacuum to yield the required product. White solid. Yield 0.65 mg (41%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.42 (s, 1H), 8.77 (s, 1H), 8.11 (dd, J = 8.6, 1.1 Hz, 1H), 7.74 (dd, J = 7.8, 1.6 Hz, 1H), 7.63 (m, 1H), 7.55 – 7.42 (m, 2H), 7.39 – 7.24 (m, 2H), 7.16 (td, J = 7.6, 1.1 Hz, 1H), 7.07 – 6.93 (m, 1H). ^{13}C NMR (DMSO-d_6 ,101MHz): δ = 152.0, 141.9, 139.2, 134.0, 133.1, 128.9, 123.0, 122.3, 121.2, 118.3, 116.9, 101.9 ppm

1-(4-Nitrophenyl)-3-(2-methylphenyl) urea U13

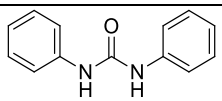
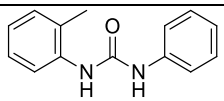
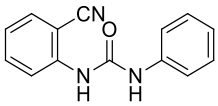
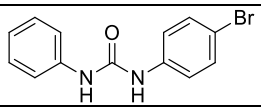
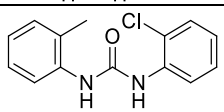
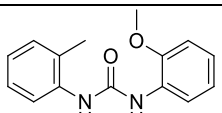
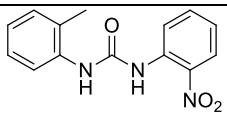
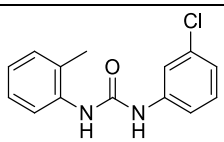
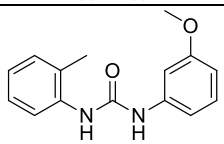
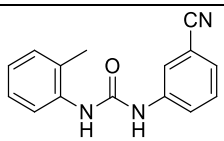
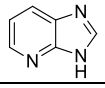
4-Nitrophenyl isocyanate (1.1g, 6.9 mmol) was dissolved in CH_2Cl_2 (25 mL) at room temperature and *o*-toluidine (0.75 g, 6.9 mmol) was added in one portion. After 5 min a white solid began to settle out. After stirring for 5 h, the white precipitate was filtered and washed with cold CH_2Cl_2 and dried under vacuum to yield the required product. White solid. Yield 1.4 g (78%).^{1}H NMR (DMSO-d_6 ,400MHz): δ = 9.64 (s, 1 H), 8.96 (s, 1 H), 8.21 (d, *J*=8.6 Hz, 1 H),

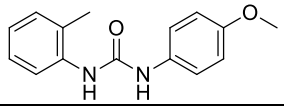
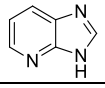
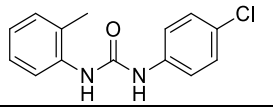
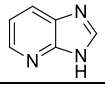
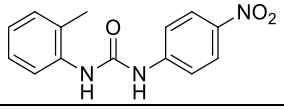
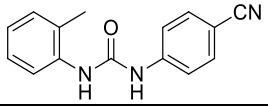
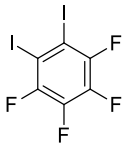
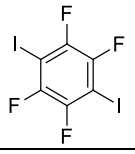
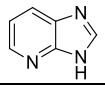
8.06 (d, *J*=8.6 Hz, 1 H), 7.65 - 7.71 (m, 1 H), 7.58 (d, *J*=8.2 Hz, 1 H), 7.14 - 7.23 (m, 3 H), 7.01 - 7.07 (m, 1 H), 2.26 ppm (s, 3 H) ^{13}C NMR (DMSO-d_6 ,101MHz): δ = 152.6, 136.7, 134.9, 134.9, 130.5, 126.3, 125.5, 124.3, 123.6, 123.2, 122.5, 18.2 ppm

Solvent-drop grinding experiments

The deazapurine (10 mg 0.083 mmol) was mixed with the urea or the halogen bond donor (0.083 mmol). Two drops of acetone was added to the mixture and ground for two minutes. The solid obtained was analyzed by FTIR.

IR data from solvent drop grinding experiments

		C=O	930-960 cm^{-1}	Co-crystal	Tautomer(based on IR)
U1		1678	939	YES	
U2		1632	953	NO	
U3		1673	942	YES	
U4		1675	935	YES	
U5		1642	950	NO	
U6		1640	951	NO	
U7		1681	938	YES	
U8		1637	935 (U8)	NO	Could no be determined due to overlaps
U9		1632	952	NO	
U10		1643	952	NO	

U11		1640	942	NO	
U12		1633	952	NO	
U13		1682	942	YES	
U14		1681	942	YES	
I1		NA	950	YES	
I2		NA	935 (I2)	YES	

Determination of tautomer based on IR

Based on the IRs of the co-crystals of which the structure has been determined it was observed that the stretch at around 950 cm^{-1} in the deazapurine shifts to around 930 cm^{-1} in all of the structures with the N7-H tautomer. No such shift was observed with the structures with the N9-H tautomer.

Syntheses for obtained co-crystals

Synthesis of 1-deazapurine ,diphenylurea (1:1), DP:U1

1-deazapurine (10 mg, 0.08 mmol) and diphenylurea were dissolved in 3 ml of acetone with heat. The solution was allowed to stand at room temperature for slow evaporation. Colourless needles were observed in three days. (m.p. 170 – 174 C^0)

Synthesis of 1-deazapurine ,1-(2-cyanophenyl)-3-phenylurea (1:1), DP:U3

1-deazapurine (10 mg, 0.08 mmol) and 1-(2-cyanophenyl)-3-phenylurea (8.91 mg 0.04 mmol) were ground together with a drop of acetone and dissolved in 3 ml methylethylketone with heat. The solution was allowed to stand at 0 ^{0}C for slow evaporation. Bronze prisms were observed in a week. (m.p.120 – 125 ^{0}C)

Synthesis of 1-deazapurine, 1-(4-bromophenyl)-3-phenylurea (1:1), DP:U4

1-deazapurine (10 mg, 0.08 mmol) and 1-(4-bromophenyl)-3-phenylurea (24.4 mg, 0.08 mmol) were dissolved in 3 ml acetone and a drop of DMSO with heat. The solution was allowed to stand at room temperature for slow evaporation. Colourless plates were observed in two weeks (m.p. 165-173 C^0)

Synthesis of 1-deazapurine ,1-(4-nitrophenyl)-3-(2-tolyl)urea (1:1), DP:U14

1-deazapurine (10 mg, 0.08 mmol) and 1-(4-nitrophenyl)-3-(2-tolyl)urea (10.19 mg 0.04 mmol) were ground together with a drop of acetone and dissolved in a mixture of 3 ml acetone, 1 ml methanol and 1 ml chloroform with heat. The solution was allowed to stand at 0 ^{0}C for slow evaporation. Yellow prisms were observed in a week (m.p. 155 -160 C^0)

Synthesis of 1-deazapurine , 1,2-diiodotetrafluorobenzene (1:1), DP:I1

1-deazapurine (2.96 mg, 0.025 mmol) and 1,2-diiodotetrafluorobenzene (10 mg, 0.025 mmol) were dissolved in 2 ml dichloromethane with heat. The solution was allowed to stand at room temperature for slow evaporation. Colourless plates were observed in 10 days (m.p.78 – 82 ^{0}C)

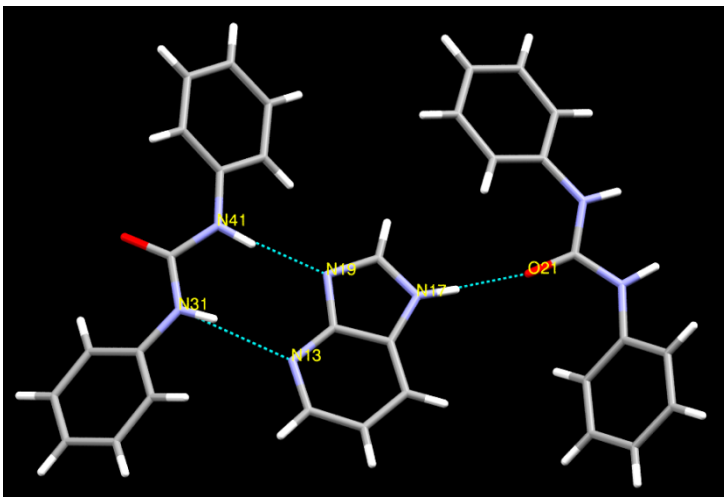
Synthesis of 1-deazapurine , 1,4-diiodotetrafluorobenzene (1:1), DP:I2

1-deazapurine (5 mg, 0.04 mmol) and 1,4-diiodotetrafluorobenzene (16.9 mg, 0.04 mmol) were dissolved in methanol with heat. The solution was allowed to stand at room temperature for slow evaporation. Bronze prisms were observed in two weeks. (m.p. 145 – 149 ^{0}C)

Structure Descriptions

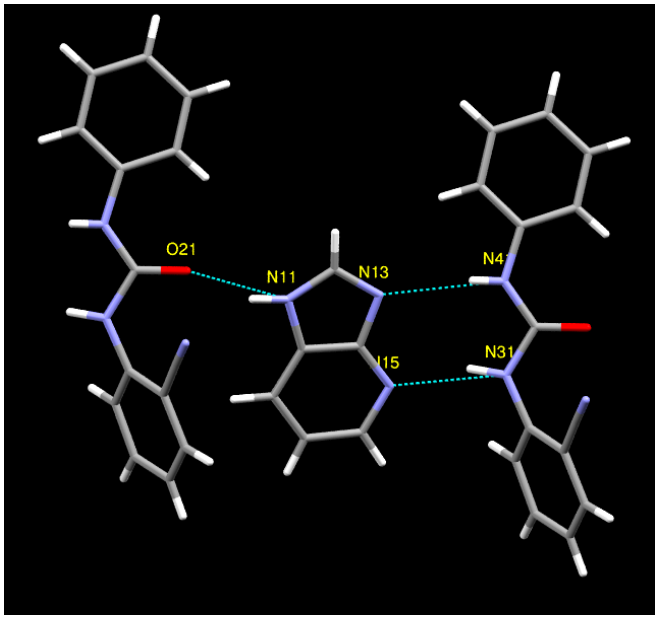
Crystal structure of 1-deazapurine ,diphenylurea (1:1), DP:U1

Structure determination of **DP:U1** shows that in the resulting 1:1 co-crystal the deazapurine exists in the N7-H tautomeric form. The two N-H groups of the urea form hydrogen bonds to the imidazole (N41-H41···N19 1.974(18) Å, N41···N19 2.8942(19) Å) and pyridyl (N31-H31···N13 2.196(19) Å, N31···N13 3.061(2) Å) nitrogens. The N-H group on the deazapurine picks up the carbonyl group (N17-H17···O21 Å, 1.81(2) N17···O21 2.7508(18) Å) at (1/2-x, 1/2+y, 1/2-z) on the urea forming a one dimensional chain.



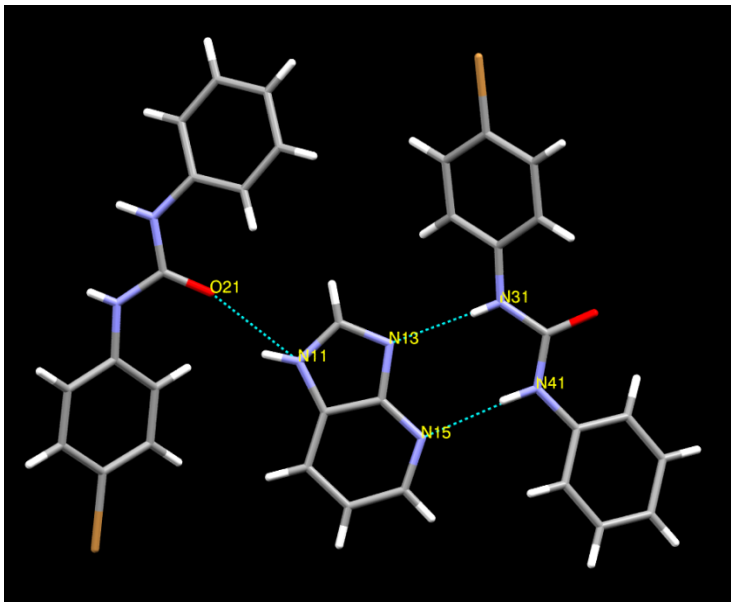
Crystal structure of 1-deazapurine ,1-(2-cyanophenyl)-3-phenylurea (1:1), DP:U3

Structure determination of **DP:U3** shows that in the resulting 1:1 co-crystal the deazapurine exists in the N7-H tautomeric form. The two N-H groups of the urea form hydrogen bonds to the imidazole (N41-H41···N13 2.13(2) Å, N41···N13 3.040(2) Å) and pyridyl (N31-H31···N15 1.98(2) Å, N31···N15 2.902(2) Å) nitrogens. The N-H group on the deazapurine picks up the carbonyl group on the urea (N11-H11···O21 1.87(2) Å, N11···O21 2.799(2) Å) at (x, -1+y, z) resulting in a one dimensional chain.



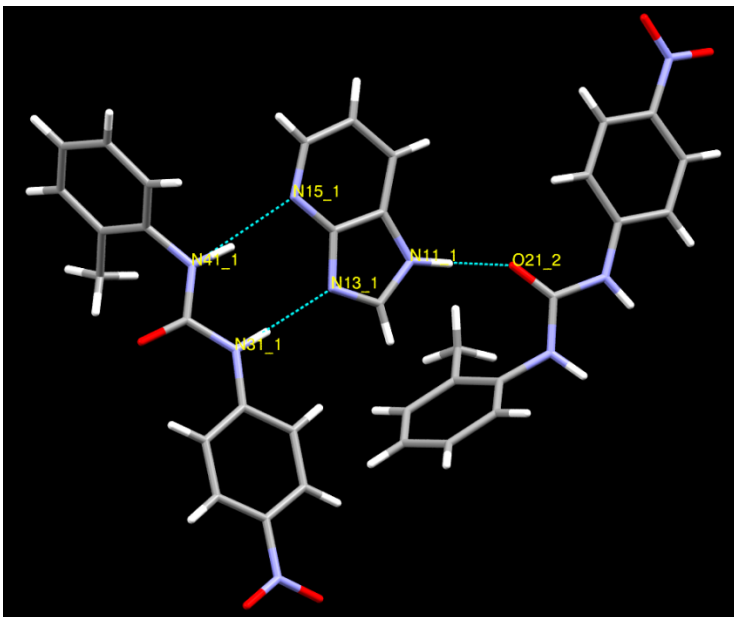
Crystal structure of 1-deazapurine , 1-(4-bromophenyl)-3-phenylurea (1:1), DP:U4

Structure determination of **DP:U4** shows that in the resulting 1:1 co-crystal the deazapurine exists in the N7-H tautomeric form. The two N-H groups of the urea form hydrogen bonds to the imidazole (N31-H31···N13 2.17(7) Å, N31···N13 2.857(6) Å) and pyridyl (N41-H41···N15 2.16(7) Å, N41···N15 3.023(6) Å) nitrogens. The N-H group on the deazapurine picks up the carbonyl group on the urea. (N11-H11···O21 1.99(7) Å, N11···O21 2.701(5) Å) at (1-x, -1/2+y, 1/2-z). resulting in a one dimensional chain.



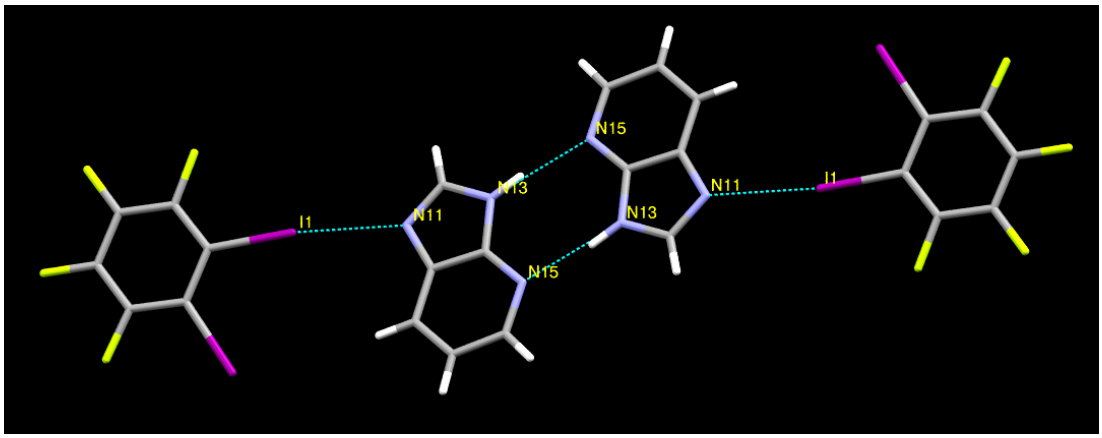
Crystal structure of 1-deazapurine ,1-(4-nitrophenyl)-3-(2-tolyl)urea (1:1), DP:U13

Structure determination of **DP:U13** shows that in the resulting 1:1 co-crystal the deazapurine exists in the N7-H tautomeric form. In the two resulting symmetrically inequivalent chains, The two N-H groups of the urea form hydrogen bonds to the imidazole (N31_1-H31_1···N13_1 2.02(4) Å, N31_1···N13_1 2.978(4) Å, N31_2-H31_2···N13_2 2.08(3) Å, N31_2···N13_2 3.005(4) Å) and pyridyl (N41_1-H41_1···N15_1 Å, 2.02(4) N41_1···N15_1 2.994(4) Å, N41_2-H41_2···N15_2 2.08(3) Å, N41_2···N15_2 3.024(4) Å) nitrogen atomss. The N-H group on the deazapurine picks up the carbonyl group on the urea (N11_1-H11_1···O21_2 Å, 1.77(4) N11_1···O21_2 2.794 (4) Å at (2-x, -y, 1-z), N11_2-H11_2···O21_1 1.85(3) N11_2···O21_1 2.803(3) Å) at (1-x, 1-y, 1-z).



Crystal structure of 1-deazapurine , 1,2-diiodotetrafluorobenzene (1:1), DP:I1

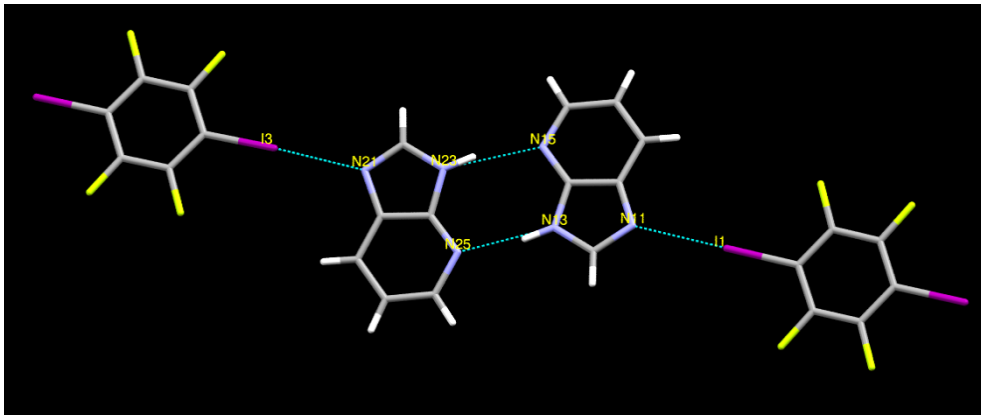
Structure determination of **DP:I1** shows that in the resulting 1:1 co-crystal the deazapurine exists in the N9-H tautomeric form. The N-H group on the deazapurine picks up the pyridine site of another deazapurine molecule forming a homodimer (N13-H13···N15 1.97 Å, N13···N15 2.843(4) Å) at (-x, 1-y, 1-z). The imidazole nitrogen forms a halogen bond to the iodine site on **I1** (I1···N11 2.800(4) Å) resulting in a zero dimensional tetramer.



Crystal structure of 1-deazapurine, 1,4-diiodotetrafluorobenzene (1:1), DP:I2

Structure determination of **DP:I2** shows that in the resulting 1:1 co-crystal the deazapurine exists in the N9-H tautomeric form. The N-H group on the deazapurine picks up the pyridine site of another deazapurine molecule forming a homodimer(N13-H13···N25 1.96 Å, N13···N25 2.828(7) Å and N23-H23···N15 1.99 Å, N15···N23 2.848(7) Å. The imidazole nitrogen forms a halogen

bond to the iodine site (I1···N11 2.777(5) Å, I3···N21 2.769(5) Å) on **I2** forming a one dimensional chain. The large peak in the difference map (4.412) peak is 0.88 Angstrom from I4. The size and location of this difference peak is not uncommon for many of our iodine-containing crystal structures.



Crystal-data table

Compound reference	DP:U1	DP:U3	DP:U4	DP:U13	DP:I1	DP:I2
Chemical formula	$(C_6H_5N_3)(C_{13}H_{12}N_2O)$	$(C_6H_5N_3)(C_{14}H_{11}N_3O)$	$(C_6H_5N_3)(C_{13}H_{11}BrN_2O)$	$(C_6H_5N_3)(C_{14}H_{13}N_3O_3)$	$(C_6H_5N_3)(C_6F_4I_2)$	$(C_6H_5N_3)(C_6F_4I_2)$
Formula Mass	331.38	356.39	410.28	390.40	520.99	520.99
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
a/Å	24.508(3)	8.6469(15)	13.5679(17)	11.7996(19)	11.5283(11)	13.0356(7)
b/Å	19.467(3)	9.9518(17)	18.536(3)	13.972(2)	14.7657(14)	23.2353(13)
c/Å	6.9054(9)	10.7848(18)	6.9157(9)	14.171(2)	8.7953(8)	9.7061(6)
α/°	90.00	76.318(9)	90.00	119.480(10)	90.00	90.00
β/°	102.327(6)	89.211(9)	93.335(7)	104.641(11)	110.886(3)	105.229(2)
γ/°	90.00	79.537(9)	90.00	93.902(11)	90.00	90.00
Unit cell volume/Å^3	3218.6(8)	886.3(3)	1736.3(4)	1915.6(5)	1398.8(2)	2836.6(3)
Temperature /K	120(2)	120(2)	120(2)	120(2)	120(2)	120(2)
Space group	C2/c	$P\bar{1}$	P21/c	$P\bar{1}$	P21/c	P21/c

No. of formula units per unit cell, Z	8	2	4	4	4	8
No. of reflections measured	13000	14318	26024	23161	19188	25846
No. of independent reflections	4476	3113	5191	6651	5009	8706
R_{int}	0.0443	0.0460	0.0804	0.0693	0.0301	0.0380
Final R1 values (I > 2σ(I))	0.0523	0.0540	0.0729	0.0740	0.0331	0.0536
Final *wR*(*F*2) values (*I* > 2σ(*I*))	0.1132	0.1549	0.1932	0.1736	0.0729	0.1471
Final *R1* values (all data)	0.0966	0.0615	0.1113	0.1207	0.0443	0.0726
Final *wR*(*F*2) values (all data)	0.1313	0.1613	0.2119	0.1978	0.0789	0.1578

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