Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Orthohalogen substituents dramatically enhance hydrogen bonding of aromatic ureas

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ADDITIONAL DATA

Intramolecular hydrogen bonding probed by FTIR spectroscopy.

Fig. S1 shows the FTIR spectra obtained for bis-ureas at 2 10^{-5} mol/L in chloroform. All compounds display two absorption bands in the range 3400 – 3450 cm^{-1} corresponding to free N-H groups and no contribution in the range 3250 – 3350 cm^{-1} expected for intermolecular hydrogen bonded N-H groups.[1] Therefore, all compounds can be considered to be monomeric at this low concentration. Interestingly, the high frequency band is located at a very similar wavenumber for all five compounds: from 3444 to 3449 cm^{-1} (Table S1). This band can be assigned to the stretching vibration of the aliphatic N-H group (N-H_β on Scheme 1),[2,3] which explains its low sensitivity to the presence of substituents on the aromatic ring. In contrast, the low frequency band is influenced by the presence of substituents on the aromatic ring and can be assigned to the stretching vibration of the aromatic N-H group (N-H_α on Scheme 1). The values for the chlorinated (3418 cm^{-1}) and brominated (3411 cm^{-1}) bis-ureas are significantly lower than for the methylated bis-urea **bMe_3** (3426 cm^{-1}). This shift is characteristic for the presence of an intramolecular interaction between the N-H_α and the halogens in ortho position.[2,3] In the case of the fluorinated bis-urea **bF_3**, the frequency value (3430 cm^{-1}) indicates the absence of intramolecular interaction or its low intensity. The absence of intramolecular hydrogen bonding to fluorine is in agreement with previous studies on similar systems,[2,3] although examples of intramolecular hydrogen bond are known in the crystalline state.[4]

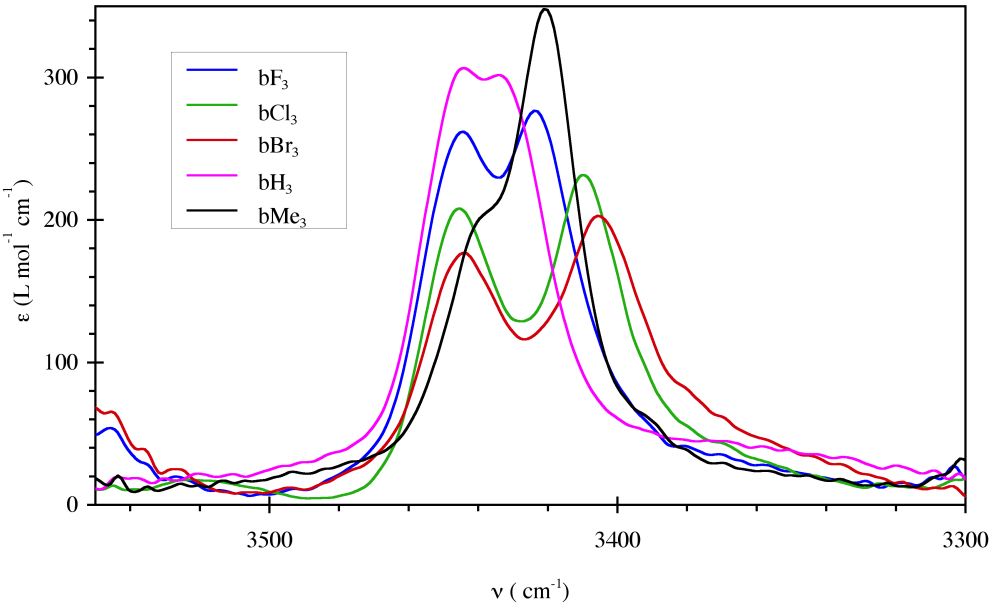
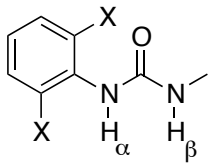


Fig. S1. FTIR spectra for bis-ureas at 2 10^{-5} mol/L in chloroform (20°C).

Conformational analysis on model mono-ureas.

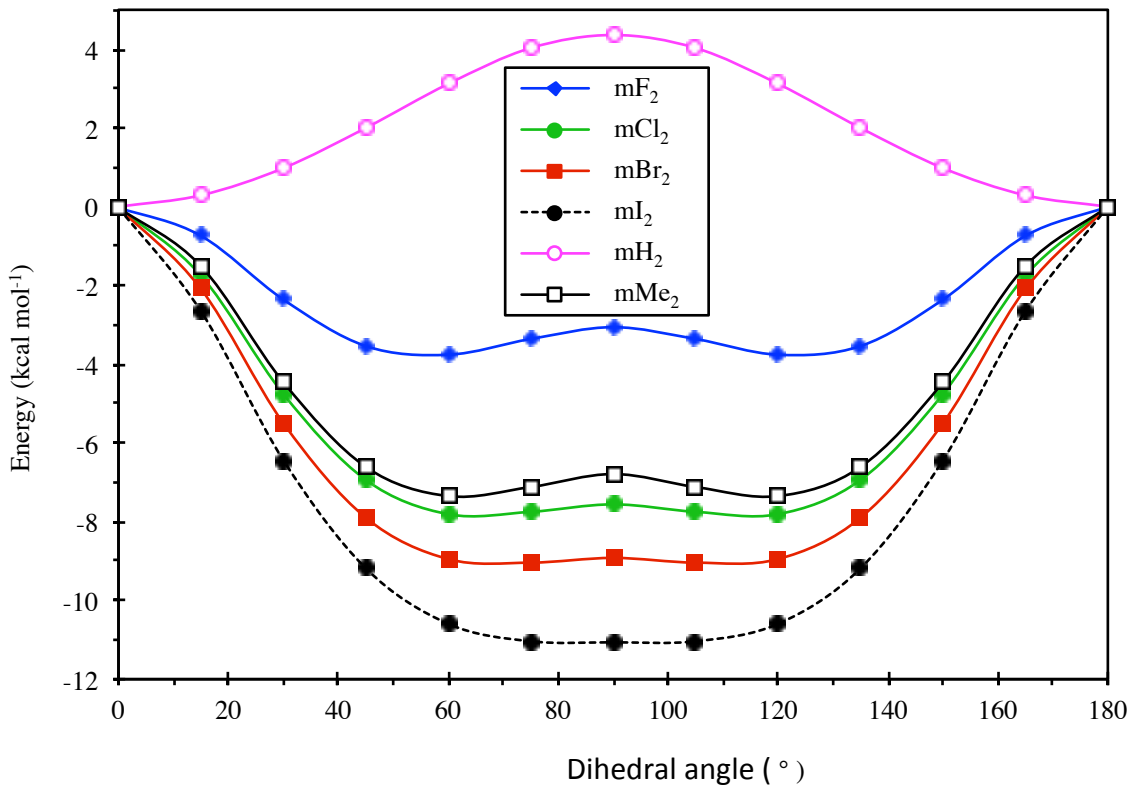


mF$_2$: X = F
mCl$_2$: Cl
mBr$_2$: Br
mI$_2$: I
mH$_2$: H
mMe$_2$: CH_3

Scheme S1. Structure of model mono-ureas.

Ab initio calculations on model mono-ureas (Scheme S1) were performed. The potential energy surfaces (Fig. S2a) reveal a strong influence of the ortho substituents on the dihedral angle (ϕ) between the urea and aromatic groups. In the absence of substituent (**mH$_2$**) the most stable conformation is coplanar (ϕ = 0). With fluorine (**mF$_2$**) or methyl (**mMe$_2$**) substituents, the most stable conformations correspond to a dihedral angle of 60 and 120°, separated by a small barrier (1 kcal/mol) at ϕ = 90°. With chlorine (**mCl$_2$**), bromine (**mBr$_2$**) or iodine (**mI$_2$**) substituents, the energy surface is completely flat from ϕ = 60 to 120°. From these most stable conformations, the N-H stretching vibration frequencies were calculated: the calculations indicate that the stretching vibration of the aliphatic N-H group (N-H$_\beta$) is insensitive to the nature of the substituent, whereas the stretching vibration of the aromatic N-H group (N-H$_\alpha$) increases in the order X = I < Br < Cl < Me < F < H. The good agreement with the experimental FTIR data (Table S1) validates this conformational analysis. Moreover, the calculated and experimental frequencies reveal that the strongest N-H$_\alpha$ / X interactions occur in the case of X = Br and Cl. This is also confirmed by the calculated distances between H$_\alpha$ and X atoms: they are all shorter than the sum of van der Waals radii, but the contact is the closest in the case of Cl and Br (Table S1).

a)



b)

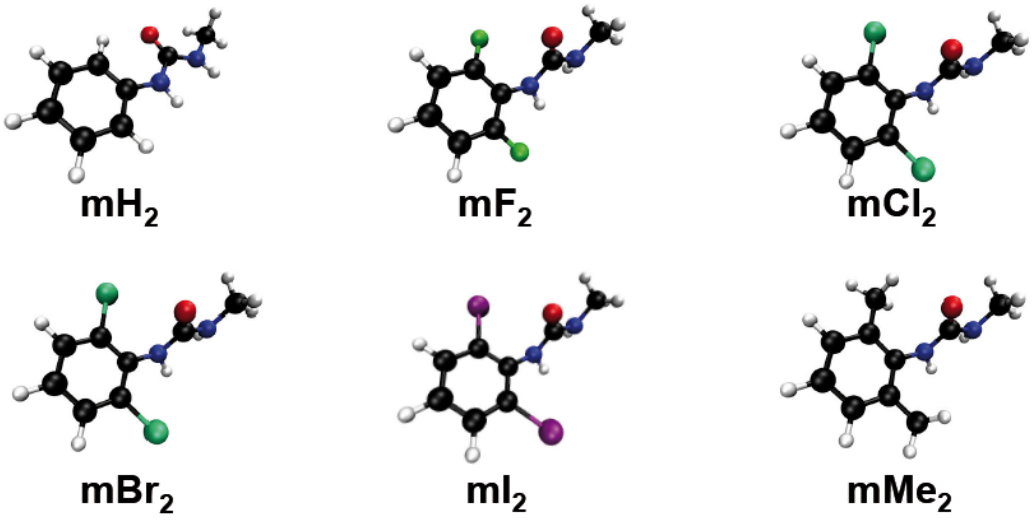


Fig. S2. (a) Potential energy surface[5] for model mono-ureas, calculated with the B3LYP functional, auc-cc-pvdz was used for all atoms except for Iodine where we used the Stuttgart Electron Core Potential and basis set. (b) Most stable conformations.

Table S1. Vibration frequencies (cm^{-1}) and distances (Å) for model mono-ureas.

substituent X	$\nu_{N\text{-}H_\alpha}$ calc,[a]	$\nu_{N\text{-}H_\alpha}$ FTIR,[b]	$\nu_{N\text{-}H_\beta}$ calc,[a]	$\nu_{N\text{-}H_\beta}$ FTIR,[b]	H_α-X distance[a]	sum of vdW radii (H+X) [a]	charge H_α [a]	charge H_β [a]
F	3489	3430	3511	3446	2.38	2.67	-0.134	-0.217
Cl	3472	3418	3512	3448	2.56	2.95	-0.133	-0.219
Br	3464	3411	3512	3449	2.66	3.05	-0.167	-0.219
I	3452	/	3505	/	2.84	3.07	-0.228	-0.227
H	3504	3434	3513	3444	2.24	-	-0.171	-0.249
Me	3488	3426	3508	3445	2.58 (C)	-	-0.165	-0.221

[a] calculated for mono-ureas (same level as described before); all the presented vibrational are the harmonic ones scaled by a factor of 0.97 to account for anharmonicities in the true potential.[6] [b] FTIR spectra for bis-ureas (2 10^{-5} mol/L in chloroform, 20°C).

Interaction between mono-ureas and DMSO or TPPO.

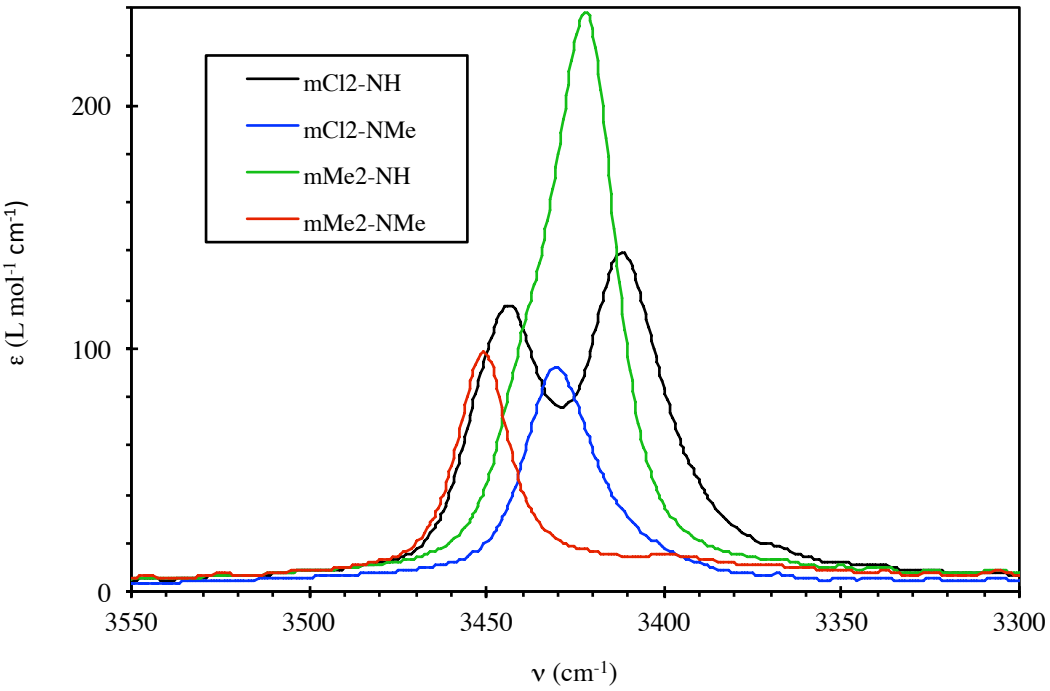


Fig. S3. FTIR spectra for mono-ureas at 5 10^{-3} mol/L in chloroform (20°C).

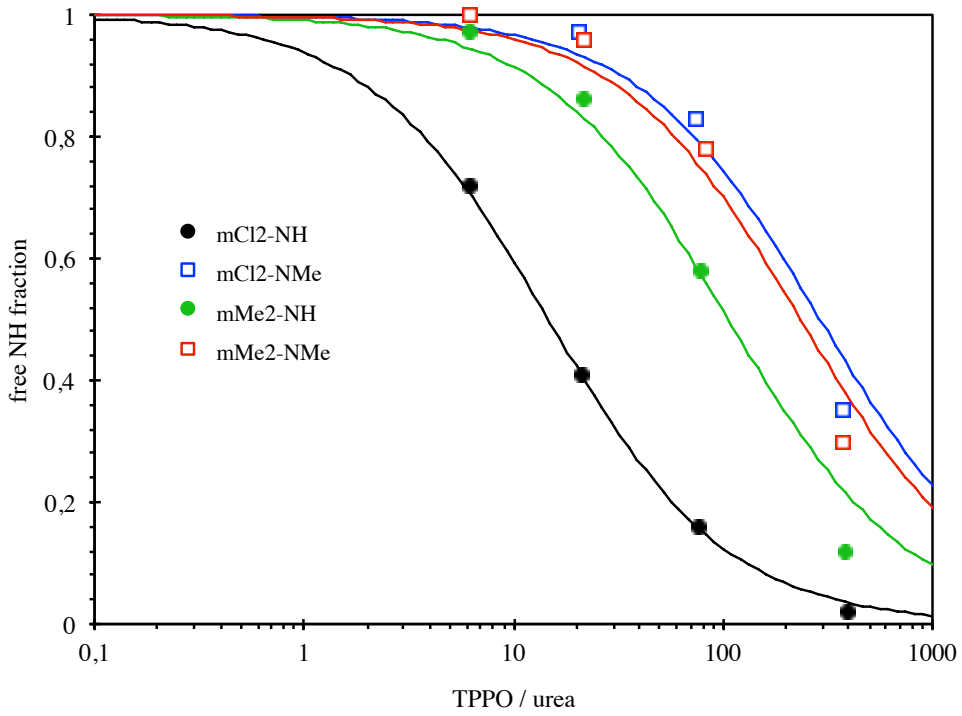


Fig. S4. Free N-H fraction determined by FTIR for mixtures of mono-ureas (5 10^{-3} mol/L) and TPPO in chloroform (20°C). The curves are fits to a 1:1 association model.

Table S2. Association constants (L/mol) determined from the fit of the data (Figs. 4 and S4) to a 1:1 association model.

	mCl_2-NH	**mMe_2-NH**	**mCl_2-NMe**	**mMe_2-NMe**
DMSO	5	0.7	0.4	0.5
TPPO	15	2	0.7	0.9

EXPERIMENTAL SECTION

Solvents were used as received. Solutions were prepared at room temperature under stirring at least 1 day prior to use.

SANS. Measurements were made at the LLB (Saclay, France) on the Paxy and Pace instruments, at several distance-wavelength combinations to cover the 6.9 10^{-3} to 0.3 $Å^{-1}$ q-range, where the scattering vector q is defined as usual, assuming elastic scattering, as $q = (4\pi/\lambda)\sin(\theta/2)$, where θ is the angle between incident and scattered beam. Data were corrected for the empty cell signal and the solute and solvent incoherent background. A light water standard was used to normalize the scattered intensities to cm^{-1} units.

The following form factor for infinitely long rigid fibrillar objects of homogeneous contrast (specific contrast, $\overline{\Delta b}^2$) and circular cross-section (radius, r) was used to fit the data represented on Fig. 2:[7]

$$I = \frac{\pi c}{q}\overline{\Delta b}^2 \frac{n_L M_0}{N_a}\left[2\frac{J_1(qr)}{qr}\right]^2$$

N_a is Avogadro number, c the concentration (g cm^{-3}), M_0 the bis-urea molar mass and J_1 the Bessel function of the first kind. The values for the specific contrast ($\overline{\Delta b}^2$) were calculated based on the estimated densities of bis-ureas and are given in Table S3. The experimental curves were adjusted by linear regression in a $\ln(qI)$ versus q^2 plot. The number n of molecule in the cross-section can be derived from n_L (the number of molecule per unit length) by assuming an average intermolecular distance of 4.6Å, which is the usual spacing for hydrogen bonded urea groups:

$$n = 4.6 \times n_L$$

Table S3. Values for the specific contrast of bis-ureas ($\overline{\Delta b}^2$) (10^{20} cm^2g^{-2}) in $CDCl_3$. Geometrical radius (r) and linear density (n_L) of the filaments, deduced from the fit shown in Fig. 2.

	bF_3	**bCl_3**	**bBr_3**	**bH_3**	**bMe_3**
$\overline{\Delta b}^2$ (10^{20} cm^2g^{-2})	2.83	2.28	1.59	4.99	5.45
r (Å)	13	12	9	12	9
n_L ($Å^{-1}$)	0.24	0.26	0.23	0.23	0.27
n	1.1	1.2	1.1	1.1	1.2

FTIR spectroscopy. Infrared spectra were recorded on a Nicolet iS10 spectrometer in a CaF_2 cell of 0.1 cm path length. The spectrum of pure solvent was subtracted.

ITC. Heats of dissociation were measured using a MicroCal VP-ITC titration microcalorimeter.[8] The sample cell (1.435 cm^3) was filled with chloroform (99% Acros, stabilized with amylene). A relatively concentrated bis-urea solution in the same solvent was placed in a 0.295 cm^3 continuously stirred (270 rpm) syringe. A first 2 μL aliquot was injected, without taking into account the observed heat, to remove the effect of solute diffusion across the syringe tip during the equilibration period. Subsequent aliquots of the solution (2-10 μL) were automatically injected into the sample cell every 200 s, until the syringe was empty.

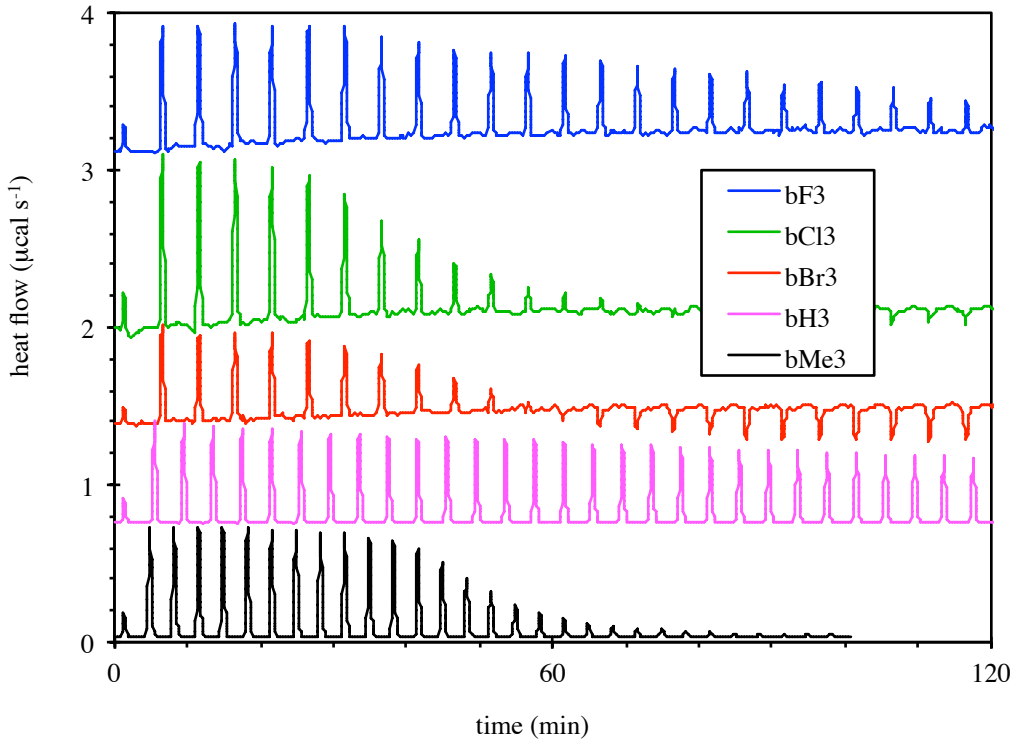


Fig. S5. Heat effect (ITC) produced by injecting aliquots of a bis-urea solution in chloroform into chloroform (T = 20°C). **bF_3**, **bCl_3** and **bBr_3**: 12 μL aliquots of a 0.3 mM bis-urea solution. **bH_3** and **bMe_3**: 10 μL aliquots of a 3 mM bis-urea solution, the heat flow was divided by 8.33 (=10/1.2) to compensate for the differences in concentration and volume.

The data displayed on Fig. 3 can be modeled according to a mass action law model describing the evolution of the concentration of monomers (M) and filaments (F_n) of any degree of polymerisation (n).[8] The values deduced from the fit for the association constants and the enthalpy of association are reported in Table S4.

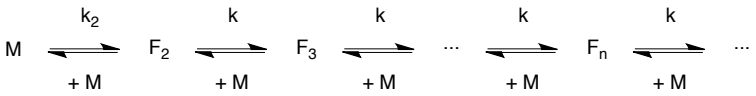


Fig. S6. Association equilibria between monomer (M) and filaments (F_n) of degree of polymerisation (n).

Table S4. Parameters deduced by fitting the ITC data shown in Fig. 3 (chloroform, 20°C).

bis-urea	c* [a] (mol/L)	k_2 [b] (L/mol)	k [b] (L/mol)	ΔG [c] (kcal/mol)	ΔH [d] (kcal/mol)	TΔS (kcal/mol)
bF_3	$1.0\ 10^{-4}$	2500	15000	-7.1	-12.4	-5.4
bCl_3	$4.1\ 10^{-5}$	1300	43000	-7.7	-12.1	-4.4
bBr_3	$5.6\ 10^{-5}$	720	29000	-7.5	-8.1	-0.6
bH_3	$1.6\ 10^{-3}$	25	1100	-5.6	-7.9	-2.3
bMe_3	$6.0\ 10^{-4}$	9.0	3200	-6.2	-6.7	-0.6

[a] concentration below which the filaments dissociate into monomers. [b] association constant for filament growth (Fig. S6). [c] free energy for filament growth ($\Delta G = -RT\ln\left(k.C_S\right)$, with C_S= 12.5 mol/L, the solvent concentration). [d] enthalpy for filament growth.

Synthesis. The synthesis of **bH_3**[9] and **bMe_3**[10] was described previously.

2,4,6-trichloro-1,3-dinitrobenzene

5.27g (0.029mol) of 1,3,5-trichlorobenzene were dissolved in 15mL of HNO_3 and the flask was kept at 40°C for 15 minutes. 13.5mL of H_2SO_4 were added and the temperature was gradually increased till 80°C in 90 minutes. The mixture was slowly poured on 350mL of water (exothermic reaction with evolution of nitrogen oxides) and this caused the precipitation of the product, which was then filtered and washed. 7.59g of a yellow powder were obtained (96%). TLC analysis confirmed the presence of only one compound ($R_f = 0.3$).

m.p. 129°C (lit. 129-130°C).[11]

GC-Mass: single peak with $[M+H]^+$ 270 (100%), 272 (97%), 274 (31%).

^{1}H-NMR (250MHz, $CDCl_3$): 7.61 (s, 1H, CH) ppm.

2,4,6-trichloro-1,3-diaminobenzene

In a 500mL flask 6.03g (0.022mol) of 2,4,6-trichloro-1,3-dinitrobenzene were dissolved in 25mL of water, 50mL of acetic acid and 80mL of ethanol. Then 7.60g (0.136mol) of iron powder were added. The flask was sonicated for 30h, and the reaction was followed by TLC. The brown mixture was filtered on silica and then washed with ethyl acetate. The filtrate was extracted twice with 200mL of KOH 2M, and this solution was washed with 200mL of ethylacetate. The organic phase was dried on Mg_2SO_4 and evaporated to give a pale yellow solid. It was crystallized in hexane to give 2.90g (62%).

GC-Mass: single peak with $[M+H]^+$ 210 (100%), 212 (97%), 214 (31%).

^{1}H-NMR (250MHz, $CDCl_3$): 7.09 (s, 1H, CH), 4.11 (br s, 4H, NH_2) ppm.

2,4,6-trifluoro-1,3-dinitrobenzene

A 50mL flask containing 2.13g (0.016mol) of 1,3,5-trifluorobenzene and 9mL of HNO_3 was kept at 40°C for 15 minutes. Then 8mL of H_2SO_4 were added and the temperature was gradually increased till 55°C in 90 minutes. The mixture was poured on 100mL of water and this caused the separation of the product, a dense liquid at the bottom of the beaker. This was isolated, washed three times with water and after this it precipitated. It was filtered, dissolved in 40mL of ethylacetate and washed with 2x40mL of brine. The solution was dried and evaporated. 2.11g of a yellow solid were obtained (yield 58%).

m.p. 54-55°C (lit. 53-55°C).[12]

GC-Mass: single peak with $[M+H]^+$ 222 (100%).

^{1}H-NMR (250MHz, $CDCl_3$): 7.16 (dt, ^3J(H,F) = 7.2 Hz, ^5J(H,F) = 1.9 Hz, 1H, CH).

^{19}F-NMR (235MHz, $CDCl_3$): -106.67 (2F, s), -121.37 (1F, s).

2,4,6-trifluoro-1,3-diaminobenzene

1.98g (0.009mol) of 2,4,6-trifluoro-1,3-dinitrobenzene were dissolved in a mixture of solvents (11mL of water, 22mL of acetic acid and 33mL of ethanol). After dissolution 2.43g (0.056mol) of iron powder were added. The flask was put in the ultrasonic bath, and the reaction was followed by TLC. After 24h, the brown mixture was filtered on silica and then washed with ethylacetate. The filtrate was evaporated and purified by flash column chromatography (silica gel, elution with ethyl acetate:hexane, 1:4). The fractions containing the product were collected to give 0.48g of a yellow solid (33%).

^{1}H-NMR (250MHz, $CDCl_3$): 6.60 (dt, ^3J(H,F) = 7.2 Hz, ^5J(H,F) = 1.9 Hz, 1H, CH), 3.38 (br s, 4H, NH_2).

2,4,6-tribromo-1,3-diaminobenzene

5.07g of *m*-phenylenediamine were dissolved in 200mL of water and bromine was added drop by drop. Immediately a grey solid appeared in the solution. After the addition of 1mL of Br_2 the mixture was filtered. This operation has been repeated twelve times on the same solution. At the end 19.33g of the crude product (black) were obtained, still containing unreacted bromine. This excess was removed by dissolution in chloroform and filtration on celite. After evaporation of the solvent 3.63g of the pure product were isolated (29%).

^{1}H-NMR (250MHz, $CDCl_3$): 7.43 (s, 1H, CH), 4.50 (br s, 4H, NH_2).

^{13}C-NMR (62.9MHz, $CDCl_3$): 141.67, 132.24, 96.32, 95.30.

Bis-ureas

In a dry 100mL flask under nitrogen atmosphere 20mL of dichloromethane and 0.0015mol of triphosgene were introduced. Then 0.002mol of the aromatic diamine and 0.004mol of diisopropylethylamine (DIEA), dissolved in 15mL of dry dichloromethane were added by a syringe pump (rate 2.5mL/h). The syringe was washed with 7mL of solvent (speed 3.5mL/h). This mixture was kept stirring for one hour and then 0.004 mol of 2-ethylhexylamine and 0.004 mol of DIEA in 12mL of

dichloromethane were added. After one night the solvent was evaporated. The raw material is a paste, which crystallises from acetonitrile.

2-Ethylhexyl-3-[3-(3-(2-ethylhexyl)ureido)-2,4,6-trichlorophenyl]urea (bCl_3)

Yield: 0.24g (30%).

^{1}H-NMR (250MHz, D_6-DMSO): 7.92 (s, 2H, NH), 7.70 (s, 1H, CH), 6.29 (br t, 2H, NH), 3.00 (br t, 4H, CH_2), 1.23 (m, 18H, CH/CH_2), 0.83 (m, 12H, CH_3).

^{13}C-NMR (62.9MHz, D_6-DMSO): 154.28, 133.83, 133.34, 130.44, 126.79, 41.85, 29.94, 27.91, 23.28, 21.86, 13.19, 10.21.

Mass ESI-TOF: $[M+Na]^+$ 543.00.

2-Ethylhexyl-3-[3-(3-(2-ethylhexyl)ureido)-2,4,6-trifluorophenyl]urea (bF_3)

Yield: 0.27g (37%).

^{1}H-NMR (250MHz, D_6-DMSO): 7.70 (s, 2H, NH), 7.21 (dt, 1H, CH), 6.30 (br t, 2H, NH), 3.00 (br t, 4H, CH_2), 1.24 (m, 18H, CH/CH_2), 0.84 (m, 12H, CH_3).

^{13}C-NMR (75MHz, D_6-DMSO): 155.59, 155.27 (ddd, ^1J(C,F) = 244 Hz, ^3J(C,F) = 7.9 Hz, ^3J(C,F) = 6.9 Hz), 154.48 (dt, ^1J(C,F) = 246 Hz, ^3J(C,F) = 7.8 Hz), 112.96 (t, ^2J(C,F) = 16 Hz), 99.80 (t, ^2J(C,F) = 26 Hz), 42.36, 30.49, 28.53, 23.78, 22.65, 14.04, 10.88.

^{19}F-NMR (282MHz, D_6-DMSO): -120.19 (2F, s), -124.27 (1F, s).

Mass ESI-TOF: $[M+Na]^+$ 495.07.

2-Ethylhexyl-3-[3-(3-(2-ethylhexyl)ureido)-2,4,6-tribromophenyl]urea (bBr_3)

Yield: 0.52g (40%).

^{1}H-NMR (250MHz, D_6-DMSO): 7.99 (s, 2H, NH), 7.90 (s, 1H, CH), 6.26 (br t, 2H, NH), 3.00 (br t, 4H, CH_2), 1.24 (m, 18H, CH/CH_2), 0.83 (m, 12H, CH_3).

^{13}C-NMR (62.9MHz, D_6-DMSO): 154.07, 136.63, 133.11, 127.41, 121.28, 41.77, 29.97, 27.94, 23.27, 21.89, 13.23, 10.23.

Mass ESI-TOF: $[M+Na]^+$ 677.05.

Mono-ureas

1-butyl-3-[2,6-dimethylphenyl]urea (mMe_2-NH)

1.5mL (0.015mol) of n-butylamine was added to 2mL (0.014mol) of 2,6-dimethylphenylisocyanate dissolved in 50mL of dry dichloromethane. After 24 hours, the solvent was evaporated and the crude solid was crystallized from acetonitrile to yield 1.9g of a white solid (59%).

^{1}H-NMR (200MHz, D_6-DMSO): 7.38 (s, 1H, NH), 7.01 (m, 3H, CH), 5.99 (t, ^3J(H,H) = 5.4Hz, 1H, NH), 3.04 (m, 2H, CH_2N), 2.14 (s, 6H, CH_3), 1.34 (m, 4H, CH_2), 0.89 (t, ^3J(H,H) = 7.2Hz, 3H, CH_3).

^{13}C-NMR Jmod (50MHz, D_6-DMSO): 156.02, 136.17, 135.58, 127.62, 125.52, 38.99, 32.18, 19.49, 18.25, 13.77.

1-butyl-1-methyl-3-[2,6-dimethylphenyl]urea (mMe_2-NMe)

1.8mL (0.015mol) of methylbutylamine was added to 2mL (0.014mol) of 2,6-dimethylphenylisocyanate dissolved in 50mL of dry dichloromethane. After 24 hours, the solvent was evaporated and the crude solid was crystallized from acetonitrile to yield 3g of a white solid (90%).

^{1}H-NMR (200MHz, D_6-DMSO): 7.61 (s, 1H, NH), 7.04 (m, 3H, CH), 3.30 (t, ^3J(H,H) = 7.2Hz, 2H, CH_2N), 2.93 (s, 3H, CH_3N), 2.16 (s, 6H, CH_3), 1.52 (m, 2H, CH_2), 1.30 (m, 2H, CH_2), 0.93 (t, ^3J(H,H) = 7.2Hz, 3H, CH_3).

^{13}C-NMR Jmod (50MHz, D_6-DMSO): 155.75, 137.02, 136.14, 127.42, 125.63, 47.58, 34.12, 29.60, 19.38, 18.14, 13.87.

1-butyl-3-[2,6-dichlorophenyl]urea (mCl_2-NH)

1.2mL (0.012mol) of n-butylamine was added to 2.15g (0.011mol) of 2,6-dichlorophenylisocyanate dissolved in 75mL of dry dichloromethane. After 24 hours, the solvent was evaporated and the crude solid was crystallized from acetonitrile to yield 2.5g of a white solid (84%).

^{1}H-NMR (200MHz, D_6-DMSO): 7.90 (s, 1H, NH), 7.47 (m, 2H, CH), 7.24 (m, 1H, CH), 6.31 (t, ^3J(H,H) = 5.7Hz, 1H, NH), 3.05 (m, 2H, CH_2N), 1.35 (m, 4H, CH_2), 0.88 (t, ^3J(H,H) = 7.1Hz, 3H, CH_3).

^{13}C-NMR Jmod (50MHz, D_6-DMSO): 154.90, 134.14, 133.86, 128.33, 127.80, 39.09, 31.97, 19.44, 13.73.

1-butyl-1-methyl-3-[2,6-dichlorophenyl]urea (mCl_2-NMe)

1.3mL (0.011mol) of methylbutylamine was added to 1.9g (0.010mol) of 2,6-dichlorophenylisocyanate dissolved in 75mL of dry dichloromethane. After 24 hours, the solvent was evaporated and the crude solid was crystallized from acetonitrile to yield 2.4g of a white solid (86%).

^{1}H-NMR (200MHz, D_6-DMSO): 8.14 (s, 1H, NH), 7.48 (m, 2H, CH), 7.27 (m, 1H, CH), 3.29 (t, ^3J(H,H) = 7.2Hz, 2H, CH_2N), 2.92 (s, 3H, CH_3N), 1.52 (m, 2H, CH_2), 1.30 (m, 2H, CH_2), 0.91 (t, ^3J(H,H) = 7.2Hz, 3H, CH_3).

^{13}C-NMR Jmod (50MHz, D_6-DMSO): 155.10, 135.07, 134.81, 128.20, 47.70, 34.16, 29.46, 19.35, 13.88.

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