Scavenging of Fluorinated *N,N'*-Dialkyl Ureas by Hydrogen Binding: A Novel Separation Method for Fluorous Synthesis.

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SUPPLEMENTARY MATERIAL

The following information is provided:

1.- The general procedures for the preparation and a listing of the physical and spectroscopic data of compounds **3** , **4a-d** and **6.**

2.- Analytical procedure for the GC-MS determination of urea **4c** impurities in the crude compounds **7a-d** and **8a-b.**

3.- FTIR spectra of **4c**, **5a** and **4c.5a** in dichloromethane and perfluorohexane.

EXPERIMENTAL PROCEDURES:

2,2,2-Trifluoroethylamine **2a** was purchased from Fluorochem

Typical Procedure for the preparation of amines **2b-d** A flask equipped with a condenser and magnetic stirrer was charged with 30% aqueous solution of NaN_3 (2.6g, 40 mmol), the corresponding 1H,1H,2H,2H-perfluoroalkyl iodide **1b-d** (20 mmol) and 5% of methyltridecylammonium chloride (Aliquat® 336) (404 mg, 1 mmol). The mixture was stirred at 90-100°C overnight, the solution was cooled to 0°C and the lower phase, consisting of pure 1H,1H,2H,2H-perfluoroalkyl azide, was separated and dissolved in dry Et_2O (150 mL). Then 10%Pd-C (150 mg) was added and the suspension was hydrogenated at room temperature and 100 psi under mechanical stirring in a 300 mL hydrogenator. After 1 h, the gases were evacuated to eliminate the nitrogen evolved in the reaction, fresh hydrogen was charged into the reactor and the hydrogenation was continued for 16h. Then, the mixture was depressurized, filtered through celite, the solvent carefully evaporated in rotavapor, and the crude distilled at normal pressure.

1H,1H,2H,2H-perfluorohexylamine **2b.** The typical procedure was followed starting from 1H,1H,2H,2H-perfluorohexyl iodide **1b** (2.63 g, 10 mmol), but neither the intermediate 1H,1H,2H,2H-perfluorohexyl azide, nor the 1H,1H,2H,2H-perfluorohexyl amine were isolated due to their high volatility. Instead, the ethereal solution of amine **2b** resulting from the hydrogenation was filtered and directly used to prepare the urea **3b**. The yield was not determined.

1H,1H,2H,2H-perfluorooctylamine **2c.** The typical procedure was followed starting from 1H,1H,2H,2H-perfluorooctyl iodide **1c** (9.48 g, 20 mmol). 1H,1H,2H,2H-perfluoroalkyl azide was formed quantitatively [^{1}H NMR($CDCl_3$ δ ppm): 3.62 (t, 2H, J= 7Hz), 2.5-2.3 (m, 2H)] and the amine **2c** was isolated as a colorless liquid. Yield: 9.59 g (88%). ^{1}H NMR($CDCl_3$ δ ppm): 3.04 (t, 2H, J= 7Hz), 2.34-2.17 (m, 2H), 1.30-1.21 (s_b, 2H). ^{13}C NMR($CDCl_3$, δ ppm): 125-140 (m), 34.7 (t, $J_{C\text{-}F}$ 21Hz), 34.3 (s_b).

1H,1H,2H,2H-perfluorododecylamine **2d.** The typical procedure was followed starting from 1H,1H,2H,2H-perfluorododecyl iodide **1d** (1.15 g, 2 mmol). 1H,1H,2H,2H-perfluorododecyl azide was formed in 87% yield [^{1}H NMR($CDCl_3$ δ ppm): 3.62 (t, 2H, J= 7Hz), 2.40 (m, 2H)] and the amine **2d** was isolated as a white solid. Yield: 0.62 g (64%, overall from **1d**). ^{1}H NMR($CDCl_3$ δ ppm): 3.08 (t, 2H, J= 7 Hz), 2.27 (m, 2H), 1.6 (s_b, 2H).

N-Isopropyl-N'-(1H,1H,2H,2H-perfluorooctyl)urea **3:** Isopropylisocyanate (98 mL, 85 mg, 1 mmol) was added dropwise to a solution of 1H,1H,2H,2H-perfluorooctylamine (399 mg, 1.1

mmol) in CH_2Cl_2 (5 mL) kept under nitrogen and the mixture was stirred at room temperature for 30 min. After that time, a gel was formed, the solvent was evaporated under vacuum to afford directly the pure product. Yield: 425 mg (95%).

General Procedure for the synthesis of ureas **4a-d:** A solution of triphosgene (2.53 g, 8.53 mmol) in CH_2Cl_2 (12 mL) was added dropwise to a stirred cold (0°C) mixture of the corresponding perfluoroalkylamine **2** (25.6 mmol), CH_2Cl_2 (64 mL) and 6M NaOH (25 mL). The stirring of the mixture was continued at room temperature for 5h, while a white precipitate was observed. The CH_2Cl_2 was evaporated directly from the mixture (rotavapor) and the solid was dissolved in diethyl ether (200 mL) and washed with brine (5 x 100 mL) until neutrality. The organic layer was dried ($MgSO_4$), evaporated and the product crystallized from methanol.

N,N'-bis-(2,2,2-Trifluoethyl)urea **4a.** The general procedure was followed, scaled to 6 mmol of amine, from 2,2,2-trifluoroethylamine (0.6 mL). The product was obtained as a white solid. Yield: 0.34 g (46 %).

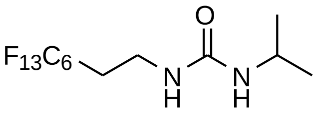
N,N'-bis-(1H,1H,2H,2H-perfluorohexyl)urea **4b.** The general procedure, scaled to 10 mmol of amine, was followed using the 1H,1H,2H,2H-perfluorohexylamine **2b** solution prepared as described above. The product was obtained as a white solid, which was crystallized from chloroform. Yield: 1.10 g (40 %, overall from iodide **1b**).

N,N'-bis-(1H,1H,2H,2H-perfluorooctyl)urea **4c.** The general procedure was followed using 1H,1H,2H,2H-perfluorooctylamine (9.3 g, 25.6 mmol). Yield: 7.89 g (82 %).

N,N'-bis-(1H,1H,2H,2H-perfluorododecyl)urea **4d.** The general procedure was followed using 1H,1H,2H,2H-perfluorododecylamine (0.56 g, 1 mmol). Yield: 0.574 g (98 %). The product was very insoluble in most organic solvents and only slightly soluble in MeOH. ^{1}H NMR(MeOD δ ppm): 2.96 (t, 4H, J= 7.5 Hz), 2.22-2.47 (m, 4H).

N,N'-bis-(1H,1H,2H,2H-perfluorooctyl)carbodiimide **6.** A suspension of N,N'-bis-(1H,1H,2H,2H-perfluorooctyl)urea **4c** (2.26 g, 3 mmol) in perfluorohexane (15 mL) was stirred in a dried flask under nitrogen at 0°C and a solution of triphenylphosphine (2.36 g, 9.0 mmol) in CH_2Cl_2 (30 mL) was added; then, bromine (0.45 mL, 1.44 g, 9 mmol) was added dropwise until a drop gave a persistent yellow color to the upper CH_2Cl_2 solution. Then, triethylamine (2.0 mL, 15 mmol) was added dropwise and the reaction was vigorously stirred at 0°C for 15 min. and at room temperature for 16h. After that time, a colorless solution was separated with a syringe and placed in another flask under nitrogen and the CH_2Cl_2 solution was washed twice with perfluorohexane (2.5 mL x 2). The perfluorohexane was evaporated in the rotavapor to afford pure carbodiimide which was stored under nitrogen at –20°C . Yield: 2.1 g (98 %).

N-Isopropyl-N’-(1H,1H,2H,2H-perfluorooctyl)urea



Reference nº
3

Mol. W. (Dalton)
448.2267

Yield (%)
95 %

Melting.P. (°C)
65-66

Molecular Formula	Elemental Analysis					
	Calculated(%)			Found(%)		
$C_{12}H_{13}F_{13}N_2O$	C 32.13	H 2.92	N 6.25	C 32.06	H 3.04	N 6.06

IR (cm^{-1}, NaCl)	3350 (NH); 1631 (C=O)
MS m/z (rel. int.)	449 (100); 434 (84.9); 388 (35.4); 363 (21.9); 345 (19.0); 44 (87.1)

^{1}H-NMR (δ, ppm) $CDCl_3$

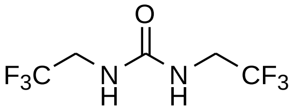
4.71 (1H, t J = 5.7Hz) CH_2-CH_2-**NH**-
4.54 (1H, d J=7.7Hz) **NH**-CH-$(CH_3)_2$
3.84 (1H, m) NH-**CH**-$(CH_3)_2$
3.60 (2H, q J= 6.4Hz) NH-$\mathbf{CH_2}$-CH_2
2.35 (2H, m) CH_2-$\mathbf{CH_2}$-CF_2-
1.15 (2H, d J= 6.6Hz) CH-$\mathbf{(CH_3)_2}$

^{13}C-NMR (δ, ppm) $CDCl_3$

157.16 (1C, s) **C**=O
105-125 (6C,m) **C**-F
42.34 (1C, s) **CH**$(CH_3)_2$
32.70 (1C, s) NH-$\mathbf{CH_2}$-CH_2
31.68 (1C, t J= 21 Hz) $\mathbf{CH_2}$-CF_2
23.35 (2C, s) CH-$\mathbf{(CH_3)_2}$

Comments:

N,N’-bis(2,2,2-trifluoroethyl)urea



Reference nº
4a

Mol. W. (Dalton)
224.1056

Yield (%)
46

Melting.P. (°C)
155-156

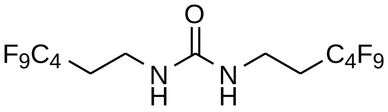
Molecular Formula	Elemental Analysis					
	Calculated(%)			Found(%)		
$C_5H_6F_6N_2O$	C 26.80	H 2.69	N 12.50	C 27.40	H 2.67	N 12.55

IR (cm^{-1}, KBr)	3356.5(NH); 3320.6 (NH); 1643.8 (C=O); 1600
MS m/z (rel. int.)	225 (41); 197 (17); 161 (13); 109 (25); 95 (46); 91 (100); 67(22).

^{1}H-NMR (δ, ppm) MeOD	^{13}C-NMR (δ, ppm) MeOD
4.82 (2H, s) **NH** 3.83 (4H,q J= 9 Hz) –**CH_2**-CF_3	159.55 (1C,s) **C=O** 126.12 (2C, q J= 278 Hz) –CH_2-**CF_3** 42.25 (2C, q J= 34.5 Hz) –**CH_2**-CF_3

Comments:
Soluble in diethylether and methanol.

N,N'-bis(1H,1H,2H,2H-perfluorohexyl)urea



Reference nº
4b

Mol. W. (Dalton)
552.205

Yield (%)
21

Melting.P. (°C)
65-66

Molecular Formula	Elemental Analysis					
	Calculated(%)			Found(%)		
$C_{13}H_{10}F_{18}N_2O$	C 28.28	H 1.82	N 5.07	C 28.62	H 1.90	N 5.24

IR (cm^{-1}, KBr)	3365 (NH); 1638.8 (C=O)
MS m/z (rel. int.)	552 (100); 534 (21); 333 (11.5); 264 (15); 244 (20); 44 (24)

^{1}H-NMR (δ, ppm) $CDCl_3$

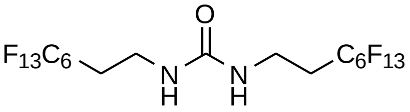
4.81 (2H,b.s) **NH**
3.55 (4H, m) NH-**CH_2**-CH_2
2.35 (4H, m) CH_2-**CH_2**-CF_2-

^{13}C-NMR (δ, ppm) $CDCl_3$

157.33 (1C,s) **C=O**
105-125 (8C, m) –**CF**
32.77 (2C,s) NH-**CH_2**-CH_2-
31.38 (2C, t J= 21 Hz) –CH_2-**CH_2**-CF_2-

Comments:

N,N’-bis(1H,1H,2H,2H-perfluorooctyl)urea



Reference nº
4c

Mol. W. (Dalton)
752.237

Yield (%)
83

Melting.P. (°C)
95

Molecular Formula	Elemental Analysis					
	Calculated(%)			Found(%)		
$C_{17}H_{10}F_{26}N_2O$	C 27.14	H 1.34	N 3.72	C 27.53	H 1.40	N 3.86

IR (cm^{-1}, KBr)	1100,1300 (CF),1581.2 (amida 2), 1637.5 (C=O), 3333.3, 3380.2 (NH)
MS m/z (rel. int.)	389(M-15)(5), 276(14), 203(40), 202(26), 138(13), 118 (100), 104(38), 73(55), 68(40)

^{1}H-NMR (δ, ppm) C_6F_{14} ($CDCl_3$, internal)

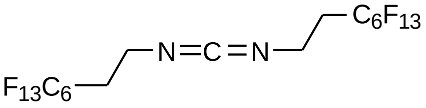
2.48 (4H, m) $-CF_3-\mathbf{CH_2}-CH_2-$
3.70 (4H, b.s) $–CH_2\mathbf{CH_2}NH-$
6.48 (2H, b.s) NH

^{13}C-NMR (δ, ppm) C_6F_{14} ($CDCl_3$, internal)

159.0
33.9
32.8

Comments:
Slightly soluble in methanol and diethylether.

N,N’-bis-(1H,1H,2H,2H-perfluorooctyl)carbodiimide



Reference nº
6

Mol. W. (Dalton)

734.22

Yield (%)
98

Melting.P. (°C)

Molecular Formula	Elemental Analysis					
	Calculated(%)			Found(%)		
$C_{17}H_8F_{26}N_2$	C	H	N	C	H	N

IR (cm^{-1}, KBr)	2134, 1248, 1235
MS m/z (rel. int.)	735 (3.5); 402 (100); 370 (11.2); 55 (22.4);

^{1}H-NMR (δ, ppm) CDCl$_3$

3.59 (2H, t J= 7Hz) =N-$\mathbf{CH_2}$-
2.29-2.5 (2H,m) –$\mathbf{CH_2}$-CF$_2$-

^{13}C-NMR (δ, ppm) CDCl$_3$

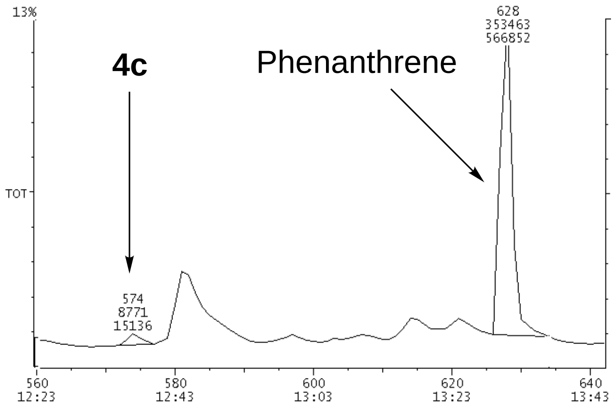
139.0	(1C, s) –N=**C**=-N-
125-105	(26C, m) –$\mathbf{C_6F_{13}}$
38.5	(2C, s, =N-$\mathbf{CH_2}$
32.3	(2C, t J=21 Hz) –$\mathbf{CH_2}$-CF$_2$-

Comments:
Colorless liquid.

ANALYTICAL PROCEDURE FOR THE GC-MS DETERMINATION OF UREA 4c IMPURITIES IN THE CRUDE COMPOUNDS 7a-d AND 8a-b.

A Finnigan GCQ GC-MS mass-spectrometer equiped with a Tracer TRB-5 (15m) column was used. Temperature program: injector (250ºC), 5min (50ºC), 15ºC/min (300ºC), 5min (300ºC). Detection limit for urea **4c** (r.t.: 12:37 min) using phenanthrene (r.t.: 13:31 min) as internal standard was 0.04ppm in the injected solution (MeOH). This value corresponds to 0.1% (w/w) of **4c** in a sample of crude **7a-d** or **8a-b** (16 mg) in 10 mL MeOH containing 0.8mg phenanthrene.

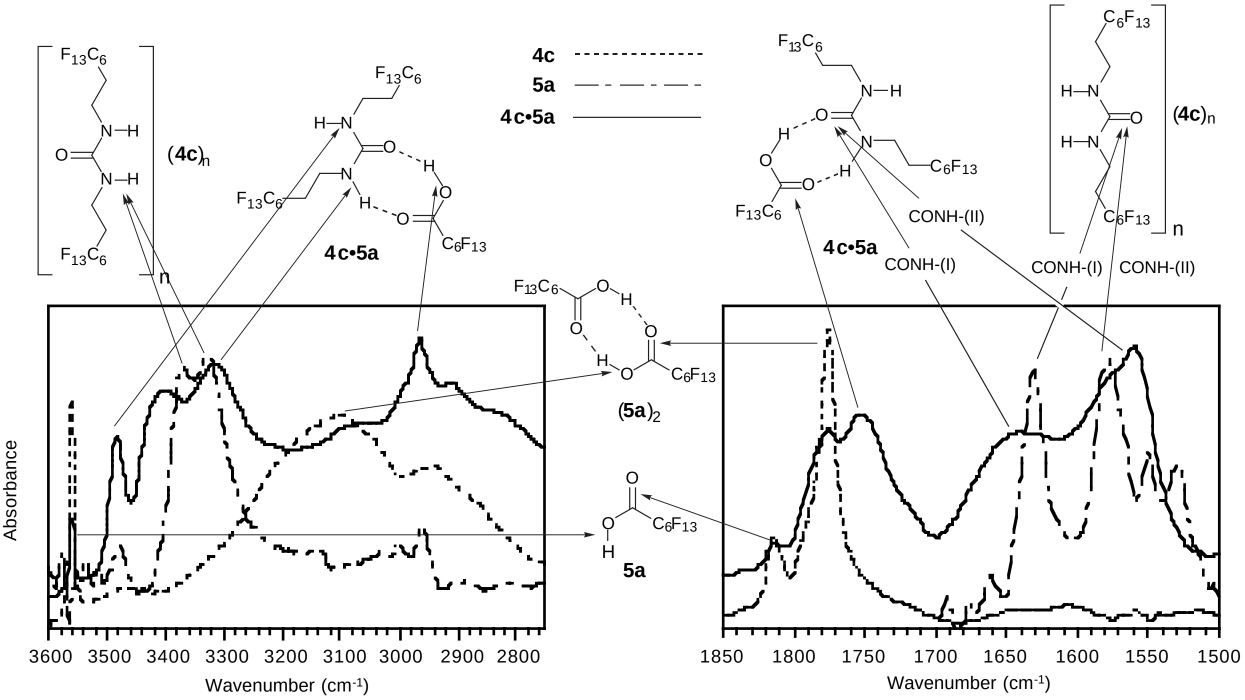
Typical chromatogram fragment from a sample of crude Cbz-Ala-Phe-OMe (**7a**): Phenanthrene peak corresponds to 1ppm and **4c** peak to 0.08ppm (0.2% in the crude sample).



FTIR SPECTRA OF 4c, 5a AND 4c.5a IN DICHLOROMETHANE AND PERFLUOROHEXANE.

A Nicolet Magna-560 FTIR-spectrometer equiped with KBr liquid windows (path lenght: 1mm) was used. Solvent-substracted spectra were recorded at 25°C (64 scans; 4 cm^{-1} resolution) on 5 10^{-3} M solutions of **4c**, **5a** and a 1:1 mixture of **4c** and **5a** in dry degassed CH_2Cl_2 and C_6F_{14} (Aldrich).

FTIR SPECTRA: NH and C=O regions recorded in C_6F_{14}



FTIR SPECTRA: NH and C=O regions recorded in CH_2Cl_2