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Scavenging of Fluorinated *N,N′*-Dialkylureas by Hydrogen Binding: A Novel Separation Method for Fluorous Synthesis

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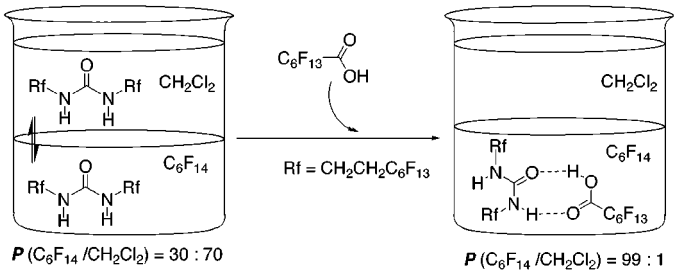
ABSTRACT



A dramatic solubility increase in fluorous solvents is observed for *N,N′*-di(polyfluoroalkyl)ureas when hydrogen binding complexes are formed with commercially available perfluoroalkanoic acid scavengers. As a case example, analytically pure peptides and esters are obtained using this novel separation method.

Fluorous Biphasic Catalysis[1] and Fluorous Synthesis[2] are ensembles of synthetic techniques based on the selective partition of perfluorinated catalysts, substrates, reagents, products, or reagent byproducts in bilayer systems consisting of an organic solvent and a "fluorous" fluid.[3] The success of such approachs relies on the efficient establishment of different phase behavior at the reaction and purification stages,[3b] which, under ideal conditions, should allow the reaction to be conducted in a homogeneous liquid phase and the purification in a multiphase (two or three) liquid system by simple separation. This criterion is fulfilled to a great extent by catalytic processes involving hydroformylation,[4] hydroboration,[5] C−C coupling,[6] and oxidations,[7] but its application to *stoichiometric* fluorous syntheses, based on phase-labeled substrates or reagents, is not trivial. Reagents labeled with "light" fluorous tags[8] (Figure 1), bearing one or two perfluorinated medium-sized chains (e.g., C_6F_{13}), are highly desirable when compared to "heavy" fluorous tags, because of their lower molecular weight and their higher solubility in polar organic solvents (**A**). However, the purification stage for "light"-tagged fluorous byproducts results in a poor separation from products (**B**). The introduc-

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(2) Suder, A.; Hadida, S.; Ferritto, R.; Kim, S. Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823−826.
(3) For reviews on this subject, see: (a) Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2057−2059. (b) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174−1196. (c) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641−650. (d) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37−41.
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(5) Juliette, J. J.; Horvath, I. T.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1610−1612.
(6) Kleijn, H.; Rijnberg, E.; Jastrzebski, J. T. B. H.; van Koten, G. *Org. Lett.* **1999**, *1*, 853−855.
(7) Klement, I.; Lütjens, H.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1454−1456.
(8) Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069−9072.

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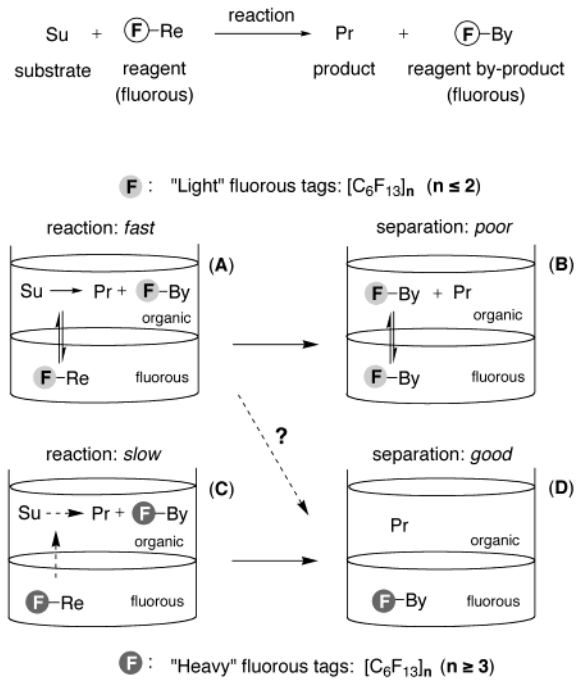


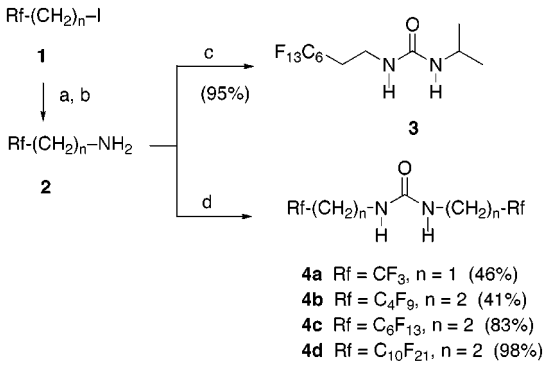
Figure 1. The reaction/separation antagonism for the stoichiometric reaction of a fluorous-labeled reagent (**F**-Re): increasing the number of perfluorinated chains improves separation but hampers the reaction.

tion of more heavily fluorinated labels is only an apparent solution to this problem, because the large number of fluorine atoms required to ensure efficient byproduct purification (**D**)[9] has liabilities in the reaction step (**C**) which becomes very slow (or does not take place at all) because it is difficult for the fluorous reagent to cross the phase boundary.[10]

Herein we report on a novel scavenging method[11] based upon the unprecedented concept of intermolecular hydrogen-binding interaction in fluorous medium[12] that improves the liquid−liquid separation step (**B**) for "light" fluorous tags. To describe the "proof-of-principle" of our strategy, we devised hydrogen acceptor/donor systems formed by *N*,*N*′-dialkylureas and perfluoroalkanoic acids. This choice was supported by the following facts: (a) *N*,*N*′-dialkylureas (i.e., *N*,*N*′-dicyclohexylurea) are the prototypical reaction byproducts of carbodiimide-promoted reactions, including the very important peptide synthesis;[13] (b) perfluoroalkanoic acids have superior hydrogen-binding capabilities than their alkyl or aryl homologues toward amide-like hydrogen acceptors;[14] and (c) perfluoroalkanoic acids are commercially available compounds.

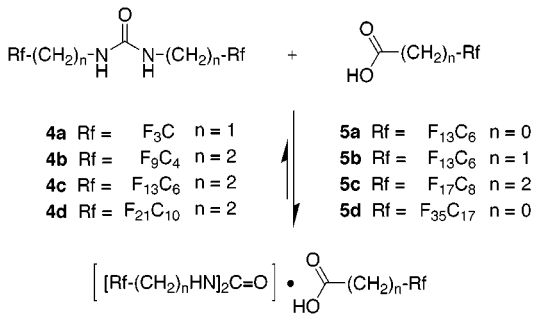
Thus, *N*,*N*′-dialkylureas **3** and **4** bearing, respectively, one and two fluorous tags were readily prepared from amines **2**[15] (Scheme 1) by addition to alkyl isocyanates or by

Scheme 1



carbonylation with triphosgene[16] in overall yields ranging from 41% to 98%. Polyfluorinated *N*,*N*′-dialkylureas **4a**−**d** were colorless or white solid compounds sparingly soluble in CH_2Cl_2 (typically, 0.3−0.6% at 25 °C) and, surprisingly, still less soluble in C_6F_{14} (<0.1%). Our finding was that ureas **4a**−**d** dissolved immediately upon the addition of 1 equiv of most of the polyfluoroalkanoic acids **5a**−**d** in a biphasic CH_2Cl_2/C_6F_{14} system (Scheme 2). The gravimetric determination of the partition coefficients $P_{C_6F_{14}/CH_2Cl_2}$ at 25 °C revealed ratios as high as 99/1 for complex **4c**·**5a**, bearing medium-size fluorinated chains (Rf = C_6F_{13}).

Scheme 2



Complex	$P_{(C_6F_{14}/\text{solvent})}$
3·**5a**	40 / 60 (CH_2Cl_2)
4a·**5a**	77 / 23 (CH_2Cl_2)
4b·**5a**	96 / 4 (CH_2Cl_2)
4c·**5a**	99 / 1 (CH_2Cl_2)
4c·**5a**	96 / 4 ($CHCl_3$)
4c·**5a**	90 / 10 (MeCN)

Complex	$P_{(C_6F_{14}/CH_2Cl_2)}$
4d·**5a**	emulsion
4c·**5b**	98 / 2
4c·**5c**	95 / 5
4c·**5d**	emulsion
4a·**5d**	83 /17

(9) Hughes, R. P.; Trujillo, H. A. *Organometallics* **1996**, *15*, 286−294.

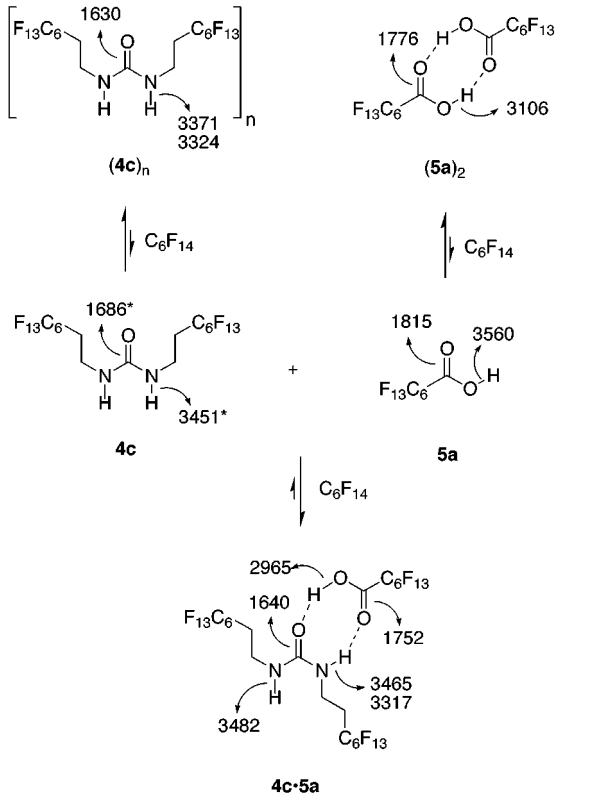
(10) Three methods have been proposed to attain a homogeneous reaction medium able to dissolve slightly polar organic substrates and fluorous reactants bearing three or more perfluorinated chains: (a) Temperature-promoted fusion of toluene/perfluorohexane or similar biphases: see ref 1. (b) Supercritical CO_2, see: Kainz, S.; Koch, D.; Baumann, W.; Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1628−1630. (c) Partially fluorinated solvents, such as benzotrifluoride (BTF), see: Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450−451.

(11) The fluorous amine $[(C_6F_{13}CH_2CH_2)_3SiCH_2CH_2CH_2]_2NH$ has been used for an automated urea synthesis as isocyanate scavenger by covalent bond formation. Linclau, B.; Sing, A. K.; Curran, D. P. *J. Org. Chem.* **1999**, *64*, 2835−2842.

Replacement of dichloromethane by more coordinating solvents, such as acetonitrile, gave moderately lower partition coefficients. Experiments to determine the minimum number of fluorine atoms in the urea component to attain an efficient partition indicated that less fluorinated ureas **4a** and **4b** gave unsatisfactory values with either medium-sized (complex **4a·5a**) or long-sized perfluoroalkanoic acids (complex **4a·5d**). On the other hand, perfluoroheptanoic acid **5a** was also more efficient than their pony-tailed counterparts **5b** or **5c** bearing, respectively, one or two methylene spacers and also than long-sized acid **5d**. Urea/acid 1:1 complexes were isolable waxy solids or viscous liquids. For instance, **4c·5a** was a stable noncrystalline solid at room temperature but dissociated slowly on heating under vacuum (90 °C/10^{-4} Torr; 4 h) allowing the quantitative recovery of the pure urea **4c** (98%) and the sublimated perfluoroheptanoic acid **5a** (96%).

Even though the precise nature of the urea−acid hydrogen bindings is not fully clear at present, a FTIR comparative analysis (Scheme 3) of 5×10^{-3} M solutions of **4c**, **5a**, and

Scheme 3

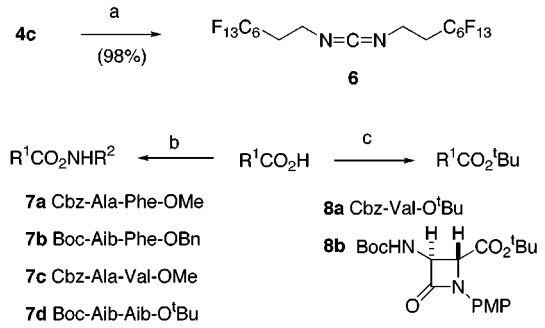


1:1 mixtures of **4c** and **5a** showed that changing the solvent from CH_2Cl_2 to C_6F_{14} dramatically enhanced the dimerization of the acid **5a**, the autoaggregation of urea **4c**, and the formation of complex **4c·5a**. Urea **4c** was present in CH_2Cl_2 essentially as a nonassociated species [3451 cm^{-1} (N−H); 1686 cm^{-1} (CONH amide-I); 1540 cm^{-1} (CONH amide-II)]. In C_6F_{14}, however, no free urea could be detected and the N−H and C═O amide-I bands shifted to lower frequencies [3371 cm^{-1} and 3324 cm^{-1} (N−H); 1630 cm^{-1} (CONH amide-I)], while the CONH amide-II band appeared at higher frequencies (1575 cm^{-1}), consistent with the formation of C═O···H−N autoaggregation bindings.

A 1:1 mixture of **4c** and **5a** in CH_2Cl_2 showed, in addition to the peaks previously mentioned, three strong bands in the carbonyl region [1752 cm^{-1} (C═O of **5a**, associated with the urea NH); 1640 cm^{-1} (CONH amide-I), 1563 cm^{-1} (CONH amide-II)], assigned to **4c·5a**. In C_6F_{14} a similar behavior was observed, but the free **4c** carbonyl band could not be detected, indicating that the equilibrium was completely shifted to **4c·5a**. Furthermore, a new band at 3482 cm^{-1} appeared, which was consistent with the free N−H stretching band present in **4c·5a**.[17]

To check the efficiency of this new separation technique for "fluorous synthesis", some exploratory reactions based on the use of the dehydrated carbodiimide counterpart of the urea **4c** were investigated (Scheme 4). Carbodiimide **6**[18]

Scheme 4[a]



[a] (a) Ph_3PBr_2, NEt_3, CH_2Cl_2/C_6F_{14}; (b) **6**, H_2NR^2; (c) **6**, HOtBu, DMAP (0.1 equiv). PMP: C_6H_4OMe-*p*.

was a stable and storable liquid, conveniently prepared by the reaction of urea **4c** with triphenylbromophosphonium bromide and triethylamine[19] in a CH_2Cl_2/C_6F_{14} biphasic

(12) Fully fluorocarbon-soluble coordination complexes of Mn(II) perfluorocarboxylates and perfluorinated triamines have been described recently. See: Vincent, J.-M.; Rabion, A.; Yachandra, V. K.; Fish, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2346−2349.

(13) For reviews, see: (a) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233−284. (b) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589−636.

(14) Crystalline adducts of linear oligomers of Nylon-6 precipitated from trifloroethanol solution with perfluoroglutaric acid, but not with nonfluorinated diacids. See: Aharoni, S. M.; Wasserman, E. *Macromolecules* **1982**, *15*, 20−25.

(15) Trabelsi, H.; Szönyi, F.; Michelangeli, N.; Cambon, A. *J. Fluorine Chem.* **1994**, *69*, 115−117. None of ureas **4a**−**d** has been described yet.

(16) Correa, A.; Denis, J.-N.; Greene, A. E. *Synth. Commun.* **1991**, *21*, 1−9.

(17) Application of the NMR titration method allowed the estimation of a weak association constant (K_a = 37 M^{-1}; 25 °C) for **4c·5a** in CD_2Cl_2 observing the shift of the NH protons in fast dynamic exchange [δ(**4c**) = 4.53 ppm; δ(**4c·5a**)= 5.01 ppm], whereas the autoaggregated nature of **4c** in C_6F_{14} ($CDCl_3$ as external standard) prevented from a reliable determination of K_a for **4c·5a**. In both solvents, no formation of complexes of higher stoichiometry than 1:1 could be detected when an excess of **5a** was added. For methods of determination of association constants by NMR, see: Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170.

solvent medium. Simple separation and evaporation of the fluorous phase afforded the pure product **6** in 98% isolated yield, thus setting the stage for the efficient recycling of urea **4c**.

Condensation reactions carried out in a biphasic CH_2Cl_2/C_6F_{14} medium proceeded to give good yields of dipeptides **7a**−**d** after being washed twice with a solution of perfluoroheptanoic acid in perfluorohexane and once again with perfluorohexane.[20] This isolation technique was also compatible with ternary systems, including acidic aqueous solutions, to separate basic compounds (i.e., 4-(*N*,*N*-dimethylamino)-pyridine), as illustrated in the case of *tert*-butyl esters **8a**,**b**. The ^{1}H NMR (500 MHz) spectra of crude products showed essentially epimerization-free pure products with no traces of fluorous byproducts, whereas a more accurate determination of fluorous urea **4c** by GC-MS analysis, using phenanthrene as internal standard, gave concentrations in the range 0.1−0.3% (Table 1).

Table 1. Condensation Reactions Promoted by Carbodiimide **6** [see ref 20]

	yield (%)	residual **4c** (%)[a]	mp (°C)	$[\alpha]^{25}$ exp. (solvent)	$[\alpha]^{25}$ lit.
7a	81	0.2	100−101	−9.0 (EtOH)	−8.3[21]
7b	85	0.2	94−95	+5.1 (CH_2Cl_2)	
7c	85	<0.1	82−84	−27.9 ($CHCl_3$)	−30.8[22]
7d	73	<0.1	oil		
8a	85	<0.1	oil	−21.5 (EtOH)	−23[23]
8b	95	0.3	55−56	+37.2 (CH_2Cl_2)	

[a] Determined by GC-MS analysis of the reaction crude.

In conclusion, the examples described here illustrate a novel solution to the reactivity/separation problem of stoichiometric "fluorous synthesis" and set the basis for further strategies based upon the new concept of fluorous chain multiplication through hydrogen binding interactions.

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Supporting Information Available: Preparation procedures and physical and spectroscopic data for compounds **3**, **4a**−**d**, and **6**, FTIR spectra of **4c**, **5a**, and **4c**·**5a**, and analytical methods to determine the purity of **7a**−**d** and **8a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For another synthesis of carbodiimide **6**, see: Trabelsi, H.; Bollens, E.; Jouani, M. A.; Gaysinski, M.; Szönyi, F.; Cambon, A. *Phosphorous, Sulfur Silicon* **1994**, *90*, 185−191.

(19) Palomo, C.; Mestres, R. *Synthesis* **1981**, 373−374.

(20) **Preparation of peptides 7a**−**d:** equimolar amounts of N-protected amino acid, α-amino ester and **6** (3×10^{-4} mol each) in CH_2Cl_2 (1 mL), and C_6F_{14} (1 mL) were stirred at room temperature for 16 h. The mixture was washed successively with perfluoroheptanoic acid (0.4 M in C_6F_{14}, 0.5 mL × 2) and C_6F_{14} (0.5 mL), and the CH_2Cl_2 phase was separated and evaporated. **Preparation of *tert*-butyl esters 8a,b:** a biphasic mixture (CH_2Cl_2/C_6F_{14}: 1.5/1.5 mL) of carboxylic acid (4.6×10^{-4} mol), *tert*-butyl alcohol (5×10^{-4} mol), 4-(*N*,*N*-dimethylamino)pyridine (5×10^{-5} mol), and **6** (5×10^{-4} mol) was stirred at room temperature for 18 h. Aqueous HCl (1 M, 1 mL) and perfluoroheptanoic acid (5×10^{-4} mol) were added, and the central CH_2Cl_2 phase was washed successively with perfluoroheptanoic acid (0.5 M in C_6F_{14}, 1 mL) and C_6F_{14}(0.5 mL). Evaporation of the CH_2Cl_2 phase gave the product.

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