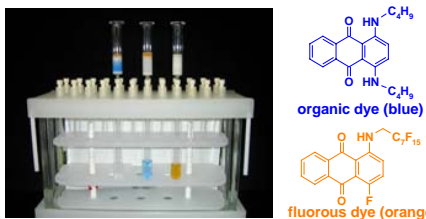


Introduction

Fluorous chemistry is a new solution-phase synthetic technology.^{1,2} Perfluoroalkyl chains are used as "phase tags" to facilitate the separation process, which is achieved by strong and selective interactions between fluororous molecules and fluororous sorbents. This presentation describes recent advances of fluororous separation techniques:

- 1) Plate-to-plate solid-phase extraction (SPE).**³⁻⁵ Pressure or gravity-driven 24-, 48- and 96-well plates SPE and water-free elution solvent systems have been developed;
- 2) Automated SPE.**⁶ F-SPE has been successfully implemented to RapidTrace SPE workstation;
- 3) Flash chromatography.** Using the Biotage FlashMaster system, we have achieved variable scale separations of fluororous intermediates in library synthesis;
- 4) Fluorous HPLC⁷** can be used for analytical and prep-scale separation of fluororous samples. It's application for fluororous mixture synthesis (FMS) and MS-directed high-throughput purification ahs also been developed.

F-SPE Demo with a Dye Mixture



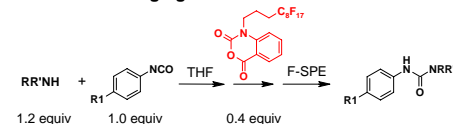
Left tube: beginning of fluorophobic wash (80:20 MeOH:H₂O)
Center tube: end of fluorophobic wash
Right tube: end of fluorophilic wash (100% MeOH)

I. Plate-To-Plate SPE

24-Well Plates 3 g Si-gel (40-60 μm), up to 0.3 g sample loading⁴



24-Parallel F-Scavenging Reactions



R ₁	H ₂ NBu	Me	Ph	OMe	Cl	MeO
	95(92)*	83(96)	95(93)	86(96)	92(91)	100(96)
	83(100)	81(99)	79(100)	81(100)	83(100)	90(100)
	100(80)	100(96)	100(97)	100(94)	100(96)	100(99)
	100(94)	100(99)	100(100)	100(100)	100(100)	100(100)

* yield% (purity% LC-MS, UV254)

96-Well Plate⁵



Gravity plate with large Si gel Positive pressure (Chem Tech)

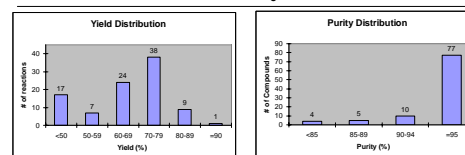
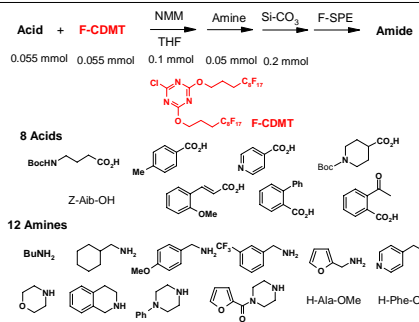
2-3 mL filtration plate; up to 75 mg sample loading; DMF and DMSO as water-free fluorophobic elution solvents

II. RapidTrace Automated F-SPE⁶



- Up to ten modular units, each unit conducts 10 SPEs
- A maximum of 100 SPEs can be finished in 1-2 h unattended
- Each SPE cartridge charged with 2 g of fluororous silica gel
- Automatic conditioning, sample loading, elution and rinsing
- Autosampler can load solution and suspension samples
- Back pressure up to 100 psi, maximum flow rate 30 mL/min
- Up to eight elution solvents and their gradient combinations

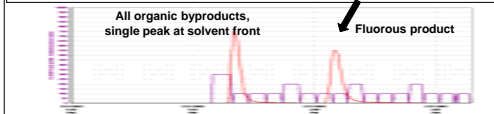
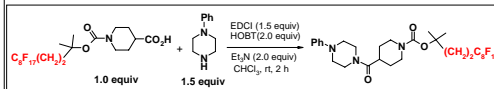
96 Parallel Amide Coupling Reactions with F-CDMT followed by RapidTrace F-SPE



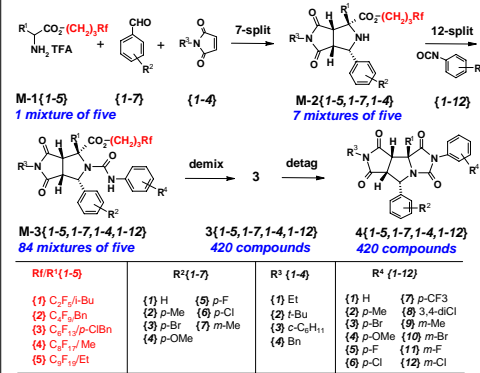
III. Large-Scale F-Flash Chromatography



variable cartridge size, UV-triggered fraction collection

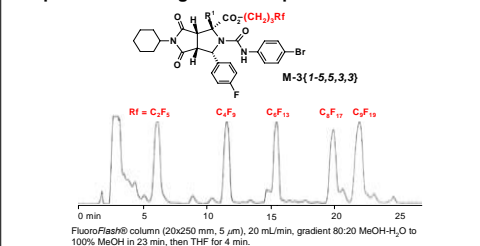


IV. F-HPLC Demixing in Mixture Synthesis⁷

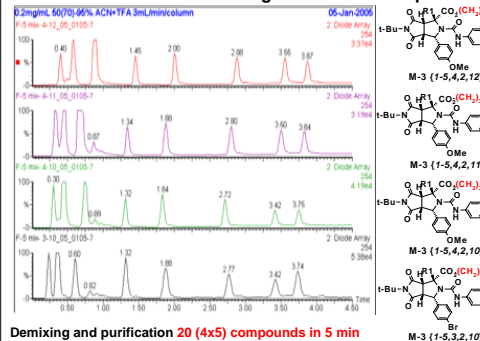


420 Ureas M-3 (84 x 5) by 91 FMS reactions (7 cycloaddition + 84 isocyanate reactions)
Could need 455 parallel reactions (35 cycloadditions + 420 isocyanate reactions)

Prep-Scale Demixing of a 5-Component Mixture



Four-Column Parallel Demixing of 4 Mixture Samples



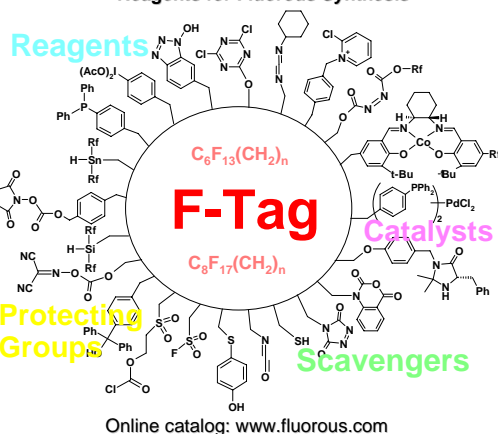
Demixing and purification 20 (4x5) compounds in 5 min

Conclusions

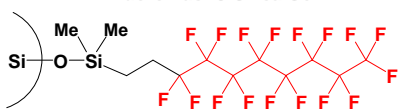
A series of fluororous silica gel-based separation techniques including plate-to-plate SPE, RapidTrace automated SPE, large-scale flash chromatography, and F-HPLC have been developed for parallel and high-throughput purifications. The strong and selective interaction between F-molecules and F-silica gel provides very efficient and reliable separations.

Acknowledgement: This work was supported by NIH GMS SBIR Grant (2R44GM067326-02).

Reagents for Fluorous Synthesis



FluoroFlash® Silica Gel



F-SPE silica gel (40-60 μm or 125-210 μm):

Selective retention of fluororous molecules

F-HPLC silica gel (5 μm): Separation of a fluororous mixture based on fluorine content

References:

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