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Chemistry in fluorous media: a user's guide to practical considerations in the application of fluorous catalysts and reagents

Luis P. Barthel-Rosa [a], J. A. Gladysz [a,b,*]

[a] *Department of Chemistry, University of Utah, Salt Lake City, UT 84112, USA*
[b] *Institut für Organische Chemie, Friedrich-Alexander Universität Erlangen-Nürnberg, Henkestrasse 42, D-91054 Erlangen, Germany*

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* Corresponding author. Fax: +49-9131-8529132.
E-mail address: gladysz@organik.uni-erlangen.de (J. A. Gladysz)

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Abstract

Fluorous solvents commonly exhibit temperature-dependent miscibilities with organic solvents. Thus, catalysts and reagents that have high affinities for fluorous solvents can be used in protocols that combine the advantages of one-phase chemistry (higher temperature) and biphase product separation (lower temperature). This review provides a 'how to' guide with respect to solvent sources, and solubility and polarity characteristics. All currently available partition coefficients for fluorous catalysts and reagents, as well as various adducts and products, are tabulated.

Keywords: Biphase product separation; Catalysts; Fluorous media; One-phase chemistry

1. Introduction

Catalyst immobilization, recovery, and re-use are among the most important frontiers of catalysis [1]. Towards these ends, a novel protocol, 'fluorous biphase catalysis', has recently been defined and developed by Horváth [2–5]. Our laboratory [4–8] and others [9] have also played key roles in this endeavor, which can be extended to reagents for stoichiometric chemistry [10], and encompasses ligand synthesis [8,11], 'tagging' strategies to facilitate target isolation from complex multicomponent mixtures [12], mechanistic studies [7] and physical measurements [13]. Some antecedents for fluorous biphase chemistry can be identified [14]. These are fully discussed in recent perspectives and more detailed reviews [1,3].

The purpose of this symposium article is not to recount the historical development of fluorous biphase chemistry, retabulate the fast-growing applications, or engage in the common practice of republishing our own work without added depth or new insight. Rather, we aim to present a 'user's guide' to selected aspects of this protocol, some of which can appear arcane to researchers who have not previously worked with or experienced the unusual properties of highly fluorinated molecules. Variants of the fluorous biphase technique are given schematically in Fig. 1, and elaborated in the following section.

2. Overview of the method

Horváth introduced the term 'fluorous' as an analog to 'aqueous' for highly fluorinated alkane, ether, and tertiary amine solvents. As summarized below, a variety of such solvents are commercially available. They commonly give bilayers with organic solvents, as illustrated in Fig. 1. As analyzed by Curran, syntheses and separations critically depend upon 'orthogonal phases' such as 'gas', 'solid', 'aqueous liquid', and 'organic liquid' [12]. Thus, fluorous media have constituted a largely unknown and greatly under-utilised orthogonal phase.

Furthermore, many organic/fluorous solvent combinations become miscible at elevated temperatures. This is illustrated in sequence 1-A in Fig. 1, and specific data are given below. Accordingly, chemistry can be effected under homogeneous *or* heterogeneous conditions (sequence 1-A vs. sequence 1-B). The first variant can combine, with suitably designed catalysts or reagents, the advantages of one-phase chemistry (higher temperature) and biphase product separation (lower temperature).

How can catalysts or reagents be engineered to have high affinities for fluorous phases? The most obvious approach is to attach fluoroalkyl groups or 'pony tails' such as $(CH_2)_y(CF_2)_xCF_3$ [2a] These serve, when of sufficient length and quantity, a 'like dissolves like' function. Similar strategies are used to design dyes capable of sticking to Teflon [15]. The $(CH_2)_y$ spacers provide tuning elements that can be adjusted to insulate the active site from the electron withdrawing fluorines (higher y values), or enhance Lewis acidity (lower y values) [2c].

Importantly, many organic compounds have relatively low affinities for fluorous phases, at least relative to organic phases. Thus, products can often be isolated in high yields by simple phase separations. Alternatively, the fluorous phase can be

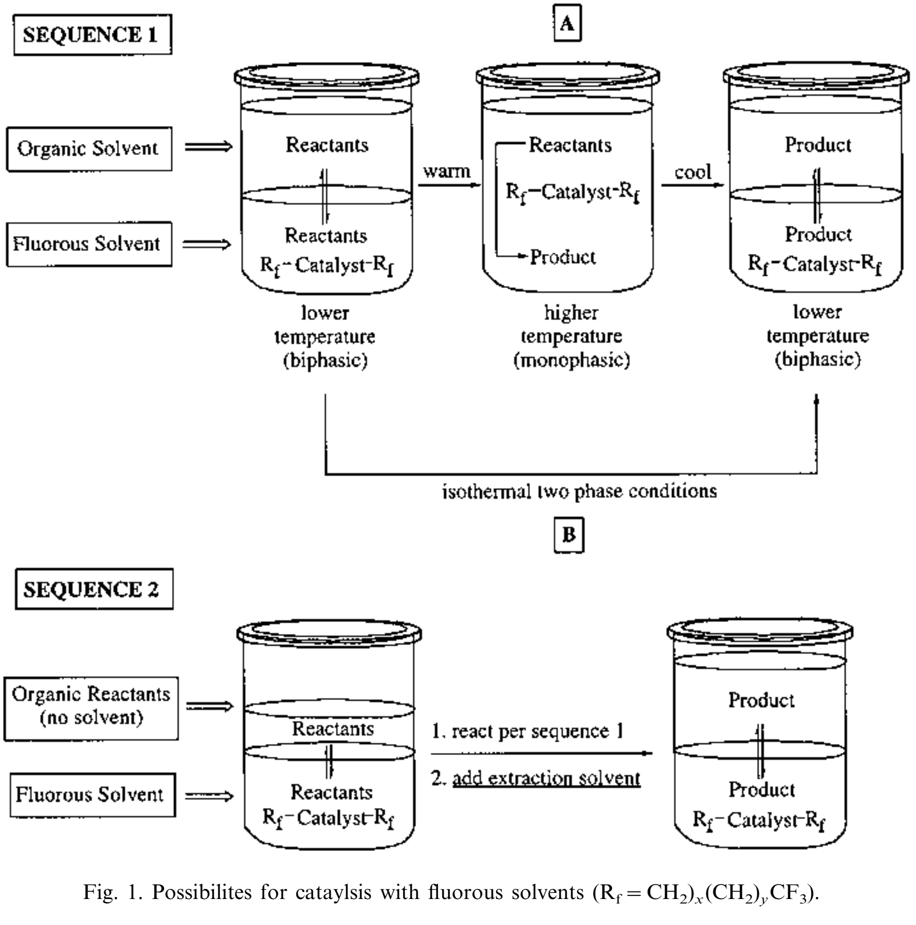


Fig. 1. Possibilites for cataylsis with fluorous solvents ($R_f = CH_2)_x(CH_2)_yCF_3$).

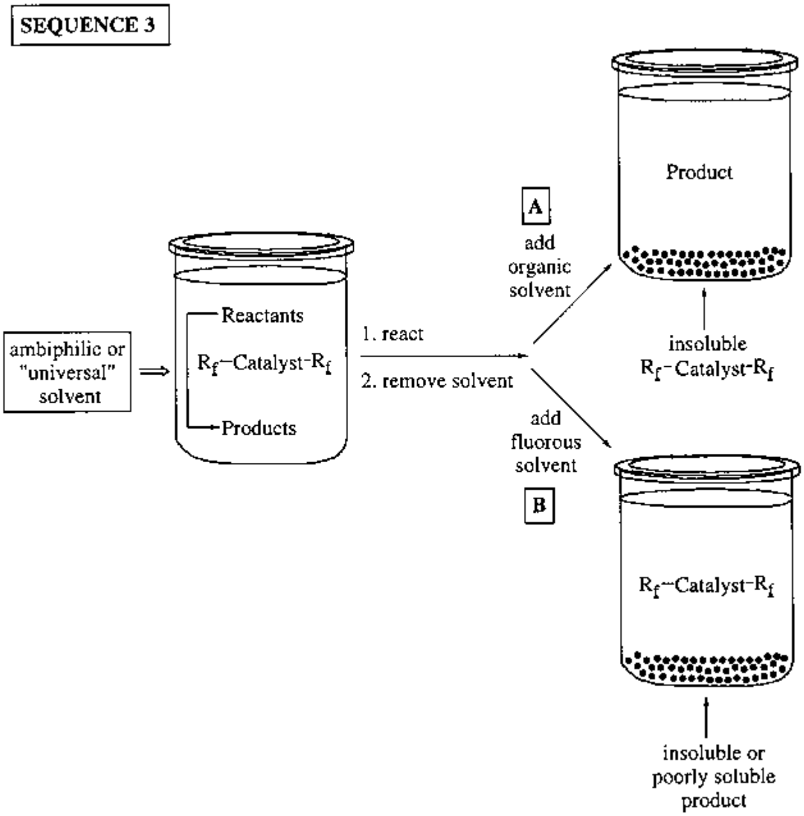


Fig. 1. (*Continued*)

extracted with additional organic solvent. Some variants of sequence 1 are also illustrated in Fig. 1. For example, an organic solvent may not be necessary during the reaction stage, as shown in sequence 2. Also, ambiphilic solvents that dissolve appreciable quantities of fluorous and non-fluorous substances exist. One example is $CF_3C_6H_5$ ((trifluoromethyl)benzene or α,α,α-trifluorotoluene) [12]. As shown in sequence 3, these also allow one phase reaction conditions. The ambiphilic solvent is then removed, and either the product or fluorous species extracted from the residue.

3. Commercial fluorous solvents

As summarized in Table 1, numerous perfluorinated solvents are commercially available. Perfluorinated alkanes are the most common, although many perfluorinated ethers and amines can also be purchased. They are sold in 80–99% purity ranges from vendors such as Oakwood Products, PCR, Fluorochem, Aldrich,

Table 1
Representative commercially available fluorous solvents

Solvent	Formula	B.p. (°C)	M.p. (°C)	Common name	CAS #	1998 vendors
Perfluoro-1,3,5-trimethylcyclohexane	MW $\approx$ 460[i]	250-260	-44.7	Galden HT110	[311-89-7]	1998 vendors
Perfluoromethylcyclohexane	$CF_3C_6F_{11}$	76.1	-44.7	PFMC	[355-02-2]	[a,b,c,d,e,f]
Perfluoro-1,2-dimethylcyclohexane	C_8F_{16}	101.5	-56	Flutec PP3	[306-98-9]	[a,b,c,d,e]
Perfluoro-1,3-dimethylcyclohexane	C_8F_{16}	101-102	-55	–	[335-27-3]	[a,b,c,d,e]
Perfluoro-1,3,5-trimethylcyclohexane	C_9F_{18}	125	–	–	[374-76-5]	[a,b,c,d]
Perfluorohexane	C_6F_{14}	57.11	-87.1	FC-72 (Flutec PP1)	[355-42-0]	[a,b,c,d,e,f]
Perfluoroheptane	C_7F_{16}	82.4	-78	FC-84	[335-57-9]	[a,b,c,d,e,f]
Perfluorooctane(s)	C_8F_{18}	103-105	–	FC-77	[307-34-6]	[a,b,c,d,e,f]
1-Bromoperfluorooctane	$C_8F_{17}Br$	142	–	–	[423-55-2]	[a,b,g]
Perfluorodecalin	$C_{10}F_{18}$	142	-10	–	[306-94-5]	[a,b,c,d,e,f]
α,α,α-Trifluorotoluene	$CF_3C_6H_5$	102	-29	Oxsol-2000	[98-08-8]	[a,g,h]
Perfluorotributylamine	$C_{12}F_{27}N$	178-180	-50	FC-43	[311-89-7]	[a,b,c,d,e,f]
Perfluorotripentylamine	$C_{15}F_{33}N$	210-220	-25	FC-70	[338-84-1]	[a,b,c,d,e,f]
Perfluorotrihexylamine	$C_{18}F_{39}N$	250-260	33	FC-71	[432-08-6]	[a,b,c,d,e,f]
Perfluoropolyether	MW $\approx$ 410[i]	70	–	Galden HT70	–	[b,c,f]
Perfluoropolyether	MW $\approx$ 388[i]	85	–	Galden HT85	–	[b,c,f]
Perfluoropolyether	MW $\approx$ 460[i]	90	–	Galden HT90	–	[b,c,f]
Perfluoropolyether	MW $\approx$ 580[i]	110	–	Galden HT110	–	[b,c,f]

[a] Oakwood products.
[b] PCR.
[c] Fluorochem.
[d] Lancaster.
[e] PRM-1.
[f] 3M.
[g] Aldrich.
[h] Oxychem.
[i] General formula $CF_3[(OCF(CF_3)CF_2)_m(OCF_2)_n]OCF_3$.

P&M-1 (based in Moscow, Russia), Lancaster, OxyChem, and 3M. A wide selection of boiling points is available, and densities are always greater than those of common organic solvents. This market has been developed in a large part to serve the electronics industry. Due to manufacturer delivery contracts, bargain-priced 55 gallon lots appear (in our experience) more frequently from obscure warehouses in Phoenix, Arizona than the vendors given above. Seasonal fluctuations in delivery times are also common.

Perfluorinated aromatic solvents are conspicuously absent from Table 1. Importantly, the sp^2 carbon–fluorine bonds and arene cloud lead to significant intermolecular dipole and induced dipole interactions [16]. Thus, perfluorinated or highly fluorinated arenes are usually miscible with organic solvents. In fact, attractive phenyl-perfluorophenyl stacking interactions are used as design elements in crystal engineering [17].

Commercial perfluorinated polyethers (PFPEs) [18] are available in four 'flavors' with the general structures $-\{[CF(CF_3)CF_2O]_m-(CF_2O)_n\}-$ (Fomblin/Galden), $-[(CF_2CF_2O)_p-(CF_2)_q]-$ (Fomblin Z), $-[CF(CF_3)CF_2O]_n-$ (Krytox), and $F-[CF_2CF_2CF_2O]_n-CF_2CF_3$ (Demnum). Note that the first and third contain chiral monomer units and will therefore consist of mixtures of diastereomers, analogous to polypropylene. The lone pairs in perfluorinated ethers and amines are extremely low in energy, such that from the standpoint of chemistry they can be considered 'invisible'.

We favor $CF_3C_6F_{11}$ (perfluoromethylcyclohexane or PFMC), a more expensive solvent, for much exploratory work and all mechanistic studies. Cheaper perfluorinated alkanes would serve equally well, but many are sold as mixtures of isomers or by boiling point range. This could compromise the reproducibility and interpretation of rate constants, partition coefficients, and related measurements. Hence, technical grades are best reserved for extractions, chromatography, or preparative reactions that have already been optimized.

4. Fluorous solvent polarity data

Perfluorinated solvents exhibit extremely low polarities. There are many ways to gauge polarity, ranging from familiar parameters such as dielectric constant and dipole moment to kinetic, equilibrium, and solventochromic measurements. As analyzed elsewhere [19,20], one of the best scales in terms of modeling the ability of a solvent to solvate or complex a solute or transition state involves the shift of the absorption maximum of a perfluoroheptyl-substituted dye. This material was optimized to be soluble in both fluorocarbons and very polar solvents such as DMSO. Over 100 solvents have been assayed [19], and some of the resulting P_S (Spectral Polarity Index) values are given in Table 2.

The data in Table 2 confirm the very low polarities of perfluorinated amines, and the much higher polarities of perfluorinated arenes. Hexafluorobenzene ranks higher than tri-*n*-butylamine, although still lower than benzene. Interestingly, highly fluorinated alcohols such as $CF_3CF_2CF_2CH_2OH$ and $(CF_3)_2CHOH$ exhibit

P_S values (9.76, 11.08) higher than those of similar non-fluorinated alcohols. This has been attributed to strong hydrogen bonding.

5. Fluorous solvent solubility data

We find it useful to distinguish between *absolute* solubilities, which are defined by a K_{sp} value or similar parameter, and *relative* solubilities, which are defined by a partition coefficient. Only the former type are discussed in this section. Unfortunately, quantitative data for the types of solutes that would be of great relevance with respect to preparative fluorous biphase chemistry appear to be scarce. For example, reference tables that would give the amount of the reactant present in the fluorous phase under the conditions of sequence 2 in Fig. 1 would be exceedingly useful.

Nonetheless, there is a reasonable literature on small molecule solubilities [21]. Many of these studies also involve miscibility measurements, as detailed in the following section. For example, a solution of perfluoroheptane that is saturated with octane contains 11.2 mol% octane at 27.5°C, 31.8 mol% octane at 60.0°C, and 45.1 mol% octane at 65.8°C [21e]. The smaller hydrocarbon heptane is approximately twice as soluble (21.4 mol%, 27.3°C), and similar to chloroform (22.4 mol%, 24.6°C). These data nicely document the strong temperature dependences of solubilities in fluorous phases.

The available literature also documents that solubility is largely determined by two parameters: solute polarity and size. The first is a familiar extension of the 'like dissolves like' paradigm. The second is uniquely important to perfluorinated solvents, which because of low intermolecular forces have large cavities (free volumes) that can accommodate small molecules. Thus—for technological reasons

Table 2
Selected solvent spectral polarity index

Solvent	Formula	Ps	Solvent	Formula	Ps
Perfluoromethylcyclohexane	$CF_3C_6F_{11}$	0.46	Methylcyclohexane	$CH_3C_6H_{11}$	3.34
Perfluoro-1,3-dimethylcyclohexane	C_8F_{16}	0.58	1,3-Dimethylcyclohexane	C_8H_{16}	3.31
n-Perfluorohexane	C_6F_{14}	0.00	*n*-Hexane	C_6H_{14}	2.56
n-Perfluorooctane	C_8F_{18}	0.55	*n*-Octane	C_8H_{18}	2.86
Perfluorodecalin	$C_{10}F_{18}$	0.99	Decalin	$C_{10}H_{18}$	4.07
Perfluorotributylamine	$(C_4F_9)_3N$	0.68	Tri-*n*-butylamine	$(C_4H_9)_3N$	3.93
Hexafluorobenzene	C_6F_6	4.53	Benzene	C_6H_6	6.95
α,α,α-Trifluorotoluene	$CF_3C_6H_5$	7.03	Toluene	$CH_3C_6H_5$	6.58
1*H*,1*H*-Heptafluoro-1-butanol	$CF_3(CF_2)_2CH_2OH$	9.76	1-Butanol	$CH_3(CH_2)_2CH_2OH$	7.62
1,1,1,3,3,3-Hexafluoroisopropanol	$(CF_3)_2CHOH$	11.08	2-Propanol	$(CH_3)_2CHOH$	7.85

Table 3
Solubility data for $^3O_2$ and H_2 (25°C, 1 atm)

Property	$CF_3C_6F_{11}$	THF	Difference
$^3O_2$ solubility (mol fraction)	0.00456[a]	0.000816[a]	Factor of ~5
$^3O_2$ solubility (mol ratio)	0.00453	0.000815	Factor of ~5
MW (g mol^{-1})	350.05	72.11	Factor of ~5
$^3O_2$ solubility (mol Kg^{-1})	0.0129	0.0112	~Equal
Density (g ml^{-1})	1.787	0.889	Factor of ~2
$^3O_2$ solubility (mol l^{-1})	0.0232	0.0100	Factor of ~2
H_2 solubility (mol fraction)	0.0012[b]	0.000274[c]	Factor of ~4.5
H_2 solubility (mol ratio)	0.00119	0.000274	Factor of ~4.5
H_2 solubility (mol Kg^{-1})	0.0034	0.0038	~Equal
H_2 solubility (mol l^{-1})	0.0061	0.0034	Factor of ~2

[a] R. Battino (Ed.), IUPAC Solubility Data Series, vol. 7, Pergamon, New York, 1981, pp. 301 and 320.

[b] C.R. Patrick, in: R.E. Banks (Ed.), Preparation, Properties, and Industrial Applications of Organofluorine Compounds, Ellis Horwood, New York, 1982, p. 333.

[c] C.L. Young (Ed.), IUPAC Solubility Data Series, vol. 516, Pergamon, New York, 1981, p. 219 (0.0014007 for n-C_7F_{16}, p. 243).

that are beyond the scope of this article—there is an extensive literature involving gas solubilities in fluorocarbons. Importantly, gas solubilities correlate with the isothermal compressibility of the solvent [22], supporting the cavity-based solubility model.

Some additional perspectives on gas solubilities are provided in Table 3. Literature data are normally compiled as mole fractions, a unit not commonly employed by preparative chemists or kineticists. These constitute the origin of the widespread statement that ‘gases are much more soluble in fluorocarbons’—a generalization appropriate with reference to water, where a strong hydrogen bonding network must be disrupted, but less so for organic solvents [23]. As shown in Table 3, the solubilities of O_2 in $CF_3C_6F_{11}$ and THF differ by a factor of 5 when expressed as mole fractions (0.00456 vs. 0.000816) or nearly equivalent mole ratios (0.00453 vs. 0.00815). However, the molecular weights of fluorocarbons tend to be higher than those of organic solvents, and with $CF_3C_6F_{11}$ and THF differ by a factor of ca. five. This gives (0.00453 mol O_2)/(350.05 g $CF_3C_6F_{11}$) and (0.000815 mol O_2)/(72.11 g THF), resulting in nearly equal molal concentrations (mol Kg^{-1}, Table 3).

The densities of fluorocarbons also tend to be higher than those of non-halogenated organic solvents, and with $CF_3C_6F_{11}$ and THF differ by a factor of two. This translates the preceding values to (0.00453 mol O_2)/(195.9 ml $CF_3C_6F_{11}$) and (0.000815 mol O_2)/(81.1 ml THF), resulting in molar concentrations that differ by a factor of slightly more than 2 (Table 3). The solubility of H_2 in $CF_3C_6F_{11}$ and THF is slightly lower (0.0012 vs. 0.000274 as mole fractions). However, the relationships between molal and molar concentrations turn out nearly the same as with O_2 (Table 3). Hence, solubility-based rate accelerations for reactions of gases in fluorous (vs. organic) solvents must by necessity be modest.

6. Fluorous solvent miscibility data

As shown in Fig. 1, fluorous chemistry can be effected under monophasic or biphasic conditions. There are also numerous possibilities for multiphasic conditions. However, it will usually be advantageous from a rate standpoint to operate under monophasic conditions. Towards this end, it is important to know the temperatures at which various solvents become miscible. Literature data [2a][9a][21c] and some of our own qualitative observations are summarized in Table 4.

With binary solvent systems, it is common to determine a 'consolute' or 'upper critical solution' temperature, above which phase separation cannot occur, whatever the composition [25]. As would be intuitively expected, consolute temperatures are usually found for ca. 50:50 mixtures. Values are given in Table 4. However, the full phase diagrams show that in other proportions, solvents can become miscible at much lower temperatures. Furthermore, consolute temperatures can be strongly affected by solutes or dissolved species. Thus, Table 4 provides at best a rough guide to a property that is in practice determined by many parameters.

Table 4
Fluorous solvent miscibility data[a]

Solvent system	Phase	Temp. (°C)	Ref.
$CF_3C_6F_{11}/CCl_4$	Two phase	RT	[21c]
	One phase	$>26.7^b$	
$CF_3C_6F_{11}/CHCl_3$	Two phase	RT	[21c]
	One phase	$>50.1^b$	
$CF_3C_6F_{11}/C_6H_6$	Two phase	RT	[21c]
	One phase	$>84.9^b$	
$CF_3C_6F_{11}/CH_3C_6H_5$	Two phase	RT	[21c]
	One phase	$>88.6^b$	
$CF_3C_6F_{11}/ClC_6H_5$	Two phase	RT	[21c]
	One phase	$>126.7^b$	
$C_8F_{17}Br/CH_3C_6H_5$	Two phase	RT	[9a]
	One phase	$50–60^c$	
$C_{10}F_{18}{}^d/CH_3C_6H_5$	Two phase	RT	[9a]
	One phase	64^c	
$CF_3C_6F_{11}$/hexane/$CH_3C_6H_5{}^e$	Two phase	RT	[2a]
	One phase	36.5^c	
$CF_3C_6F_{11}$/hexane	Two phase	0^c	[24d]
	One phase	RT	
$CF_3C_6F_{11}$/pentane	Two phase	-16^c	[24d]
	One phase	RT	
$CF_3C_6F_{11}$/ether	Two phase	0^c	[24d]
	One phase	RT	

[a] All data for a 1:1 volume ratio unless otherwise stated.

[b] Consolute temperature.

[c] Experimental observation; not a consolute temperature.

[d] Perfluorodecalin.

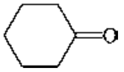
[e] Volume ratio 1:3:3.

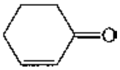
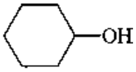
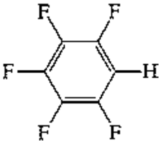
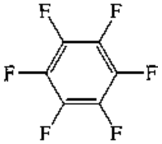
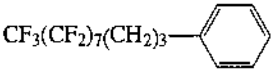
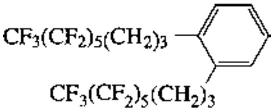
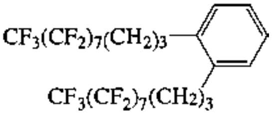
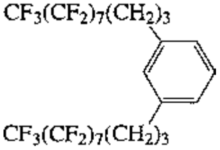
It is worth emphasizing that liquid biphase systems often contain both components in each phase. One familiar example is ether/water, where drying agents are needed to render the ether layer anhydrous after separation. With toluene/$CF_3C_6F_{11}$ at 25°C, we measure ratios of 98.4:1.6 (molar), 94.2:5.8 (mass) and 97.1:2.9 (volume) in the upper organic layer, and 3.8:96.2, 1.0:99.0 and 2.0:98.0 in the lower fluorous layer [4b]. Given that solutes would alter these ratios, we have to date approximated biphase systems as immiscible components that retain their original volumes. This assumption underlies all of the partition coefficient measurements presented in the following sections.

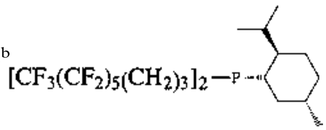
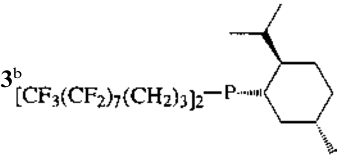
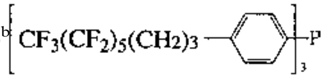
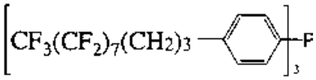
7. Partition coefficients—measurement

The rational isolation of products from fluorous biphase reactions requires some knowledge of the partition coefficient. The optimization and design of fluorous catalysts and reagents likewise requires partition coefficient data. To our knowledge, only a few partition coefficients involving fluorous and organic phases have been measured. All of the data that we are currently aware of are collected in Chart 1. These include unpublished results from our own laboratory [24].

Chart 1. List of measured partition coefficients for fluourous modified substances[a]

Entry	Substance	Solvent system	Partitioning % organic:fluorous	Method	Ref.
1	$CH_3(CH_2)_8CH_3$	$CH_3C_6H_5:CF_3C_6F_{11}$	94.6:5.4	GLC	[24a]
2	$CH_3(CH_2)_9CH_3$	$CH_3C_6H_5:CF_3C_6F_{11}$	95.8:4.2	GLC	[24a]
3	$CH_3(CH_2)_{10}CH_3$	$CH_3C_6H_5:CF_3C_6F_{11}$	96.6:3.4	GLC	[5]
4	$CH_3(CH_2)_{11}CH_3$	$CH_3C_6H_5:CF_3C_6F_{11}$	97.6:2.4	GLC	[24a]
5	$CH_3(CH_2)_{12}CH_3$	$CH_3C_6H_5:CF_3C_6F_{11}$	98.1:1.9	GLC	[24a]
6	$CH_3(CH_2)_{14}CH_3$	$CH_3C_6H_5:CF_3C_6F_{11}$	98.9:1.1	GLC	[24a]
7	$CH_3(CH_2)_7CH{=}CH_2$	$CH_3C_6H_5:CF_3C_6F_{11}$	95.2:4.8	GLC	[24a]
8	$CH_3(CH_2)_8CH{=}CH_2$	$CH_3C_6H_5:CF_3C_6F_{11}$	96.3:3.7	GLC	[24a]
9	$CH_3(CH_2)_9CH{=}CH_2$	$CH_3C_6H_5:CF_3C_6F_{11}$	97.5:2.5	GLC	[5]
10	$CH_3(CH_2)_{10}CH{=}CH_2$	$CH_3C_6H_5:CF_3C_6F_{11}$	98.1:1.9	GLC	[24a]
11	$CH_3(CH_2)_{11}CH{=}CH_2$	$CH_3C_6H_5:CF_3C_6F_{11}$	98.4:1.6	GLC	[24a]
12	$CH_3(CH_2)_{13}CH{=}CH_2$	$CH_3C_6H_5:CF_3C_6F_{11}$	99.1:0.9	GLC	[24a]
13		$CH_3C_6H_5:CF_3C_6F_{11}$	97.8:2.2	GLC	[5]

14		$CH_3C_6H_5$:$CF_3C_6F_{11}$	98.3:1.7	GLC	[5]
15		$CH_3C_6H_5$:$CF_3C_6F_{11}$	98.4:1.6	GLC	[5]
16		$CH_3C_6H_5$:$CF_3C_6F_{11}$	77.6:22.4	GLC	[24b]
17		$CH_3C_6H_5$:$CF_3C_6F_{11}$	72.0:28.0	GLC	[24b]
18		$CH_3C_6H_5$:$CF_3C_6F_{11}$	50.5:49.5	GLC	[24a]
19		$CH_3C_6H_5$:$CF_3C_6F_{11}$	26.3:73.7	GLC	[24a]
20		$CH_3C_6H_5$:$CF_3C_6F_{11}$	8.8:91.2	GLC	[24a]
21		$CH_3C_6H_5$:$CF_3C_6F_{11}$	9.3:90.7	GLC	[24a]
22	$CH_3(CH_2)_7(CH_2)_3I$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	49.3:50.7	GLC	[24a]
23	$CH_3(CH_2)_7(CH_2)_3$**N**H_2	$CH_3C_6H_5$:$CF_3C_6F_{11}$	30.0:70.0	GLC	[24c]
24	$[CH_3(CF_2)_7(CH_2)_3]_2$**N**H	$CH_3C_6H_5$:$CF_3C_6F_{11}$	3.5:96.5	GLC	[24c]
25	$[CH_3(CF_2)_7(CH_2)_3]_3$**N**	$CH_3C_6H_5$:$CF_3C_6F_{11}$	$<0.3:>99.7$	GLC	[24c]
26^b	$[CH_3(CF_2)_5CH_2CH_2]_3$**P**	$CH_3C_6H_5$:$CF_3C_6F_{11}$	1.2:98.8	GLC	[8]
27^b	$[CH_3(CF_2)_7CH_2CH_2]_3$**P**	$CH_3C_6H_5$:$CF_3C_6F_{11}$	$<0.3:>99.7$	GLC	[8]
28^b	$[CH_3(CF_2)_9CH_2CH_2]_3$**P**	$CH_3C_6H_5$:$CF_3C_6F_{11}$	$<0.3:>99.7$	GLC	[8]
29^b	$[CF_3(CF_2)_7(CH_2)_3]_3$**P**	$CH_3C_6H_5$:$CF_3C_6F_{11}$	1.2:98.8	GLC	[8]
30^b	$[CF_3(CF_2)_7(CH_2)_4]_3$**P**	$CH_3C_6H_5$:$CF_3C_6F_{11}$	1.1:98.9	GLC	[8]
31^b	$[CF_3(CF_2)_5CH_2CH_2]_3$**P**=O	$CH_3C_6H_5$:$CF_3C_6F_{11}$	$<0.3:>99.7$	GLC	[8]

32^b		$CH_3C_6H_5$:$CF_3C_6F_{11}$	21.6:78.4	GLC	[6a]
33^b		$CH_3C_6H_5$:$CF_3C_6F_{11}$	63:93.7	GLC	[6a]
34^b		$CH_3C_6H_5$:$CF_3C_6F_{11}$	79.0:21.0	GLC	[24b]
35^b		$CH_3C_6H_5$:$CF_3C_6F_{11}$	31.8:68.2	GLC	[24b]
36^c	$[CF_3(CF_2)_5CH_2CH_2]_3\mathbf{Sn}H$	C_6H_5:$CF_3C_6F_{11}$	2.2:97.8	Gravametric	[26]
37^c	$[CF_3(CF_2)_5CH_2CH_2]_3\mathbf{Sn}H$	MeOH:$CF_3C_6F_{11}$	3.0:97.0	Gravametric	[26]
38^c	$[CF_3(CF_2)_5CH_2CH_2]_3\mathbf{Sn}H$	CH_2Cl:$CF_3C_6F_{11}$	4.7:95.3	Gravametric	[26]
39^c	$[CF_3(CF_2)_5CH_2CH_2]_3\mathbf{Sn}H$	EtOAc:$CF_3C_6F_{11}$	10.4:89.6	Gravametric	[26]
40^c	$[CF_3(CF_2)_5CH_2CH_2]_3\mathbf{Sn}H$	$CHCl_3$:$CF_3C_6F_{11}$	14.1:85.9	Gravametric	[26]
41	$[CF_3(CF_2)_5CH_2CH_2]_3COH$	THF:C_6F_{14}	9.1:90.9 (4.2:95.8)^d	Not given	[9g]
42	$[CF_3(CF_2)_5CH_2CH_2]_2C$-$(OCH_3)CH(OH)C_6H_5$	THF:C_6F_{14}	19.2:80.8	Not given	[9g]
43	$[\{CF_3(CF_2)_5(CH_2)_2\}_3P]_2$-$\mathbf{Ir}(Cl)(CO)$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	<0.3:>99.7	^{31}P-NMR	[7b]
44^e	$[\{CF_3(CF_2)_5(CH_2)_2\}_3P]_2\mathbf{Ni}$-$Cl_2$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	1.2:98.8	ICP-AES^f	[13d]
45^b	$[\{CF_3(CF_2)_5(CH_2)_2\}_3P]_3$-$\mathbf{Rh}Cl$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	0.14:99.86 (1:696)	ICP-AES^f	[4b]
46^b	$[\{CF_3(CF_2)_7(CH_2)_2\}_3P]_3$-$\mathbf{Rh}Cl$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	0.12:99.88 (1:811)	ICP-AES^f	[4b]
47^c	$[CF_3(CF_2)_9(CH_2)_2C_5H]$-$\mathbf{Mn}(CO)_3$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	35.7:64.3	IR	[13a]

48[e]	$[CF_3(CF_2)_9(CH_2)_2C_5H]\mathbf{Rh}(CO)_3$	$CH_3C_6H_5{:}CF_3C_6F_{11}$	55.5:44.5	ICP-AES[f]	[13d]
49[e]	$[CF_3(CF_2)_9(CH_2)_2C_5H_4]$- $\mathbf{Rh}(CO)$-$[P\{(CH_2)_2(CF_2)_5CF_3\}_3]$	$CH_3C_6H_5{:}CF_3C_6F_{11}$	3.3:96.7	ICP-AES[f]	[14d]
50[c]	$[CF_3(CF_2)_9(CH_2)_2C_5H_4]_2\mathbf{Fe}$	$CH_3C_6H_5{:}CF_3C_6F_{11}$	4.8:95.2	Gravimetric	[14c]
51[c]	$[CF_3(CF_2)_5(CH_2)_2C_5H_4]_2\mathbf{Zr}Cl_2$	$CH_3C_6H_5{:}CF_3C_6F_{11}$	4.6:95.4	Gravimetric	[28]
52[c]	$[CF_3(CF_2)_5(CH_2)_2C_5H_4]_2\mathbf{Zr}Me_2$	$CH_3C_6H_5{:}CF_3C_6F_{11}$	12.5:87.5	Gravimetric	[28]

[a] All measurements obtained at 27°C unless otherwise stated.

[b] 27°C

[c] Ambient temperature implied

[d] −45°C

[e] 20°C

[f] Inductivety coupled plasma—atomic emission spectrometry

Measurement techniques deserve comment at the outset. First, it is obviously important to allow sufficient time for equilibrium, and acquire data at thermostated temperatures. Analyses are best kept rigorously anaerobic. For example, we found that competing oxidations of fluorous phosphines to phosphine oxides compromised the data in exploratory experiments.

For compounds that partition approximately equally between fluorous and non-fluorous phases, accurate gravimetric determinations are easily performed. For compounds that exhibit highly biased partition coefficients, other methods are required. We favor gas chromatography (GLC), which is easily quantified, whenever possible. Multiple injections from each phase should be made and averaged. The retention time provides an independent check on analyte identity. However, care must be taken when a GLC peak is assigned to a perfluorocarbon C_xF_y or similar species. These do not give high response factors with flame ionization detectors, and the identity of eluent should be verified by mass spectrometry.

Atomic absorption spectroscopy (AA) is a very sensitive technique that is particularly suitable for fluorous coordination compounds. However, consider the toluene/$CF_3C_6F_{11}$ partition coefficient of $ClRh[P(CH_2CH_2R_{f8})_3]_3$ (entry 46, Chart 1), which is 1:811 by rhodium atomic absorption analysis. Although the apparent concentration of the analyte in toluene is low, we remain suspicious that the result is still too high. By color, there is no detectable solubility of the compound in toluene under any conditions. Importantly, atomic absorption does not provide an independent check of analyte identity. One speculative possibility is that even through the analyte qualifies as analytically pure, there remains a small contaminating quantity of an extractable rhodium by-product such as $ClRh(COD)[P(CH_2CH_2R_{f8})_3]$.

8. Partition coefficients—analysis

Entries 1–6 in Chart 1 give partition coefficients (toluene/$CF_3C_6F_{11}$) for *n*-alkanes (decane through hexadecane), and entries 7–12 give data for the corresponding terminal alkenes. The alkanes, although non-polar, show very high affinities for the toluene phase. The coefficients increase monotonically with alkane size (94.6:5.4 for decane to 98.9:1 for hexadecane). The *n*-alkenes have slightly greater toluene phase affinities, consistent with their slightly greater polarities. A comparable monotonic trend is found (95.2:4.8 to 99.1:0.9).

Entries 13–15 give partition coefficients (toluene/$CF_3C_6F_{11}$) for three much more polar compounds: cyclohexanone, cyclohex-3-en-1-one, and cyclohexanol. They also exhibit very high toluene phase affinities. As expected, the ratios increase with polarity (97.8:2.2 to 98.4:1.6). Entries 16 and 17 give analogous data for pentafluorobenzene and hexafluorobenzene. These also preferentially partition into toluene (77.6:22.4 and 72.0:28.0). As analyzed above, fluorinated arenes are good solutes for moderately polar solvents. At the same time, these two analytes show the highest fluorous phase concentrations of all the preceding compounds in Chart 1.

Entries 18–21 give analogous data for benzenoid compounds with one or two 'pony tails'. One $CF_3(CF_2)_7CH_2CH_2CH_2$ substituent gives a ca. 50:50 partition coefficient. Two *ortho* or *meta* substituents (entries 20, 21) give ca. 10:90 partition coefficients. When the fluorous segment of the pony tail is shortened (entry 19), the fluorous phase affinity decreases. Based upon these data, we have adopted a working design premise that at least three pony tails will be required to effectively immobilize benzenoid compounds.

Entries 22–25 give analogous data for an iodide and a series of $CF_3(CF_2)_7CH_2CH_2CH_2$ substituted primary, secondary, and tertiary amines. The fluorous phase affinities of the amines increase monotonically from 30.0:70.0 to 3.5:96.5 to the point where no GLC detectable concentration in toluene remains ($< 0.3: > 99.7$). Thus $(CF_3(CF_2)_7CH_2CH_2CH_2)_3N$ represents the first highly immobilized fluorous base. Importantly, amines see extensive use in catalysis.

Entries 26–33 give analogous data for a series of $CF_3(CF_2)_x(CH_2)_y$ substituted phosphines and phosphine oxides. Several trends are apparent. First, as the lengths of the $(CF_2)_x$ segments increase (entries 26–28, $x = 5$, 7, 9), the partition coefficients increase from 1.2:98.8 to $< 0.3: > 99.7$. The actual coefficients for $(CF_2)_7$ and $(CF_2)_9$ may be higher, but the amounts remaining in the organic phase are subject to detection limits as described above. Interestingly, the absolute solubilities of these compounds in $CF_3C_6F_{11}$ progressively decrease (qualitative measurements). We observe similar trends with other fluorous compounds. Such solubility decreases are common as molecules approach macromolecular limits.

Entries 27, 29 and 30 show that as the $(CH_2)_y$ spacer segment is lengthened, increased quantities of phosphine are found in the toluene phase. These compounds also exhibit a marked accompanying increase of absolute solubilities in toluene. Entry 31 shows that phosphine oxides have higher fluorous phase affinities than the corresponding phosphines. Entries 32 and 33 show that when one of the pony tails in entry 26 or 27 is replaced by a monoterpene C_{10} chiral auxiliary (menthyl), toluene phase affinities increase.

Entries 34 and 35 give analogous data for some model fluorous triaryl phosphines. With one p-$CF_3(CF_2)_5CH_2CH_2CH_2$ group on each ring, the toluene phase affinity is slightly higher (79.0:21.0). With one p-$CF_3(CF_2)_7CH_2CH_2CH_2$ group on each ring, the fluorous phase affinity is slightly higher (31.8:68.2). These results suggest that more than two pony tails will be required on each aryl ring to immobilize a triaryl phosphine, consistent with the conclusion from entries 18–21 above.

Entries 36–41 give data for a tin hydride [26] and tertiary alcohol that have ‘fluorous volumes’ close to that of the phosphine in entry 26. Similarly high fluorous phase affinities are observed. Interestingly, the hydride appears to partition into non-fluorous solvents of intermediate polarity (entries 39, 40) to a greater extent than solvents of low or high polarity (entries 36, 37).

The very high partition coefficients for the rhodium tris(fluorous phosphine) complexes in entries 45 and 46 were analyzed above. Entries 43 and 44 show that iridium and nickel bis(phosphine) analogs of the complex in entry 45 have lower fluorous phase affinities. Entries 47–52 give data for piano-stool and metallocene complexes in which each cyclopentadienyl ligand bears one pony tail [13a,c,d,27]. The metallocenes preferentially partition in the fluorous phase (12.5:87.5 to 4.55:95.45). This suggests that metallocenes with 4-6 pony tails will have very high fluorous phase affinities.

9. Publishing standards

There is an explosive growth of fluorous biphase chemistry in the literature. In this section, we suggest publication standards derived from the preceding themes that we believe will aid the development of the field. First, the partition coefficient for the fluorous catalyst or reagent should be measured, either with the biphase system utilized or a suitable reference. Analytical issues should be carefully considered, especially with regard to replicate measurements and significant digits. While it may be difficult to quantify partition coefficients of $<1:>99$, species with partition coefficients less biased than 10:90 are obviously poor candidates for fluorous biphase chemistry.

Second, the best work will also analyze for the loss of the fluorous catalyst or reagent under the reaction conditions. For example, Curran has demonstrated high levels of recovery of fluorous tin reagents in a variety of transformations [28]. Knochel has reported a fluorous ruthenium catalyst for olefin oxidation that can be recovered in 95% yield after several cycles [9a]. The catalyst of Horváth, fluorous hydroformylation, which in the absence of an alkene exhibits a $HRh(CO)[P(CH_2CH_2R_{f6})_3)]_3$ rest state [2c], shows a 4.2% loss over nine cycles. However, a more informative measure is loss as a function of turnover or product produced. In this light, the hydroformylation catalyst gives 1.18 ppm rhodium loss per aldehyde formed. We and Horváth have described a rhodium hydroboration catalyst that is similarly effective [4].

Third, it is important to keep in mind that catalyst recycling does not necessarily demonstrate high levels of catalyst recovery. Consider a three cycle series in which TON values of 1000, 1000, and 1000 are achieved. Suppose the first cycle is allowed to proceed for 1 h, but conversion is complete after 5 min. Suppose that half of the catalyst is lost in each cycle. However, even with just 25% of the catalyst remaining in the third cycle, reaction would still be complete (assuming that the rate law in no more than first order in catalyst) within 1 h. Thus, it is important to measure turnover *frequencies*, especially if catalyst loss is not separately analyzed.

10. Other issues

Several important issues that are beyond the scope of this article deserve brief mention. First, there is increasing precedent for carbon–fluorine bond oxidative additions involving coordinatively unsaturated metal fragments [29]. Fortunately, we see no evidence for such deactivation pathways in extensive studies with sixteen-valence-electron rhodium and iridium complexes, either involving the solvent or the fluorous ligand [7]. However, the design of degradation resistant fluorous ligands may become important at some future date. In a similar vein, much remains to be learned about the design and optimization of pony tails, especially with regard to solubility characteristics.

Saturated fluorocarbons usually present few toxicity problems, as evidenced by their extensive use in household cookware [30]. However, they can present environmental issues, especially with regard to large-scale commercial applications. One important parameter is environmental half life, which is estimated as 4.1×10^3 years for C_5F_{12}, and 3.1×10^3 years for C_6F_{12} [31]. Another issue is ozone depletion. Here, many perfluorinated compounds are much less problematic than chlorofluorocarbons, and the preliminary prognosis favorable for fluorous solvents and chemistry [32].

11. Experimental

11.1. Partition coefficients

The following is representative [8]. A 1 dram vial was charged with $(CF_3(CF_2)_5CH_2CH_2)_3P$ (0.0390 g, 0.0364 mmol), $CF_3C_6F_{11}$ (2.000 ± 0.015 ml), and toluene (2.000 ± 0.015 ml), capped with a mininert valve, vigorously shaken (2 min), and immersed (cap-level) in a 35°C bath. After 12 h, the bath was removed. After 1 h (ambient temperature 24°C), the vial was taken into a drybox (27°C).

After 1 h, 0.400 ± 0.005 ml aliquots of each layer were added to stock solutions of hexadecane in hexane (2.000 ± 0.015 ml, 0.00222 M). GLC analysis showed 8.52×10^{-5} mmol and 7.11×10^{-3} mmol of $(CF_3(CF_2)_5CH_2CH_2)_3P$ in the toluene and $CF_3C_6F_{11}$ aliquots, for a 98.8(0.5):1.2(0.5) ratio (7 injections averaged for two runs). The total amount of $(CF_3(CF_2)_5CH_2CH_2)_3P$ calculated from these data (0.0386 g or 0.0360 mmol using a 2.000/0.400 volume multiplier) is in close agreement with that utilized.

11.2. Rhodium leaching [4b]

A 6 dram vial was charged with $[(CF_3(CF_2)_5CH_2CH_2)_3P]_3RhCl$ (0.0302 g = 0.000926 g of rhodium, 9.00×10^{-3} mmol, 0.112 mol%), $CF_3C_6F_{11}$ (2.5 ml), norbornene (0.7602 g, 8.07 mmol), catecholborane (1.013 g, 8.45 mmol), and a stir bar. The vial was sealed and moved from an inert atmosphere glove box to a 45°C bath. The sample was stirred (3 h) and returned to a glove box, and $CF_3C_6F_{11}$ (7.50 ml) and toluene (10.00 ml) were added. The vial was vigorously shaken (5 min). After 15 min (27°C), a toluene aliquot (8.0 ml) was removed by syringe. Fresh toluene (8.0 ml) was added and the vial was vigorously shaken. After 15 min, a second toluene aliquot and a $CF_3C_6F_{11}$ aliquot (8.0 ml each) were removed. Analysis by ICP-AES as described elsewhere [2c] indicated 0.20, 0.20, and 46.9 ppm (0.0000017, 0.0000014, and 0.000838 g; 91% mass balance) of rhodium. An analogous experiment with $[(CF_3(CF_2)_7CH_2CH_2)_3P]_3RhCl$ (0.0383 g = 0.000926 g of rhodium, 9.00×10^{-3} mmol, 0.111 mol%) gave 0.10, 0.10, and 49.8 ppm (0.0000009, 0.0000007, and 0.000890 g; 96% mass balance) of rhodium. Additional details are supplied elsewhere [4b].

12. Conclusion

The preceding data and summaries should help researchers new to the field of fluorous chemistry execute published procedures and develop new reactions and applications. We plan to continually update the charts and tables, and encourage other investigators to communicate unpublished results. Chart 1 in particular represents a valuable resource. The partition coefficients therein have heretofore been fragmented among many publications, and provide an important foundation for the future design of new fluorous catalysts and reagents, and the ongoing development of the field.

Acknowledgements

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