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Introduction

Fluorous chemistry: from biphasic catalysis to a parallel chemical universe and beyond

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Abstract—The development of the title discipline is briefly summarized, and the general topics of the articles in this issue introduced. Definitions are proposed for the terms 'fluorous', 'fluorous medium', 'fluorous separation technique', 'fluorous tag', 'fluorous reaction component', 'fluorous reaction', and 'fluorous chemistry'. © 2002 Elsevier Science Ltd. All rights reserved.

The title of this Tetrahedron Symposium-In-Print, 'Fluorous Chemistry', features a word that was not in the vocabulary of chemists 8 years ago, or to our knowledge anywhere in the scientific literature. Where did this term 'fluorous' come from, and what does it mean today?

New fields and new terminology nearly always have gestation periods. Vogt, a graduate student with Keim at the University of Aachen, defended a conceptually fascinating PhD thesis in 1991 with the title 'Zur Anwendung Perfluorierter Polyether bei der Immobilisierung homogener Katalysatoren' (The application of perfluorinated polyethers for the immobilization of homogeneous catalysts). In 1993, Zhu at 3M reported the use of perfluorocarbon reaction solvents to effect azeotropic separations. Both of these studies would have made fitting contributions to this issue, but neither author used the word 'fluorous', and the former was not published or available in abstract form until 1999. Most would agree that this field was born with a seminal article by Horváth and Rabai (*Science*, **1994**, *266*, 72), and the even wider-ranging underlying patent filed earlier. The *Science* paper described a general concept, 'fluorous biphase catalysis', and impressively established its applicability to an important process, rhodium-catalyzed hydroformylation. It also introduced the concept of a 'ponytail' as a control element for phase affinity and electronic properties, and exploited the highly temperature-dependent miscibilities of organic and perfluorinated solvents.

The already broad vista opened by Horvath and Rabai was expanded almost immediately as fluorous techniques were extended from the separation of products and catalysts to the separation of products and reagents, and ponytails of varying fluorine content were used to tag libraries of compounds. Soon, ponytails got a haircut—in length and/or quantity—and were christened 'fluorous tags' (or 'fluorous labels'). New separation techniques of fluorous solid-phase extraction and fluorous chromatography sprouted to disentangle tagged molecules from non-tagged molecules and from each other. Recent work has even shown that the fluorous solvent normally required for catalyst/reagent recovery can be eliminated. The field now extends from fluorous nanoparticles on the materials side to fluorous peptides and enzymatic reactions on the biological side, and several companies are actively marketing fluorous reagents and separation media. However, there is no need for a detailed summary, because the 36 outstanding papers contained in this issue vividly convey the breadth, vitality, and excitement of the field.

The fluorous field has evolved so far beyond its incarnation that it is literally time to 'come up for air' (as we presume the famous fluorocarbon-submerged mouse must someday do), and reassess and update its vocabulary. In coining the term 'fluorous', Horváth and Rabai envisioned a word that could be used analogously to 'aqueous' or 'aqueous media'. But usage dictates definitions, and early researchers rapidly expanded usage to include fluoroalkyl-labeled species, and this sense dominates in current practice. We espouse the simplicity offered by the title of this issue, 'Fluorous Chemistry', and propose the following definition of the adjective fluorous:

> of, relating to, or having the characteristics of highly fluorinated saturated organic materials, molecules or molecular fragments. Or, more simply (but less precisely), 'highly fluorinated' or 'rich in fluorines' and based upon sp^3-hybridized carbon.

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This liberal definition subsumes the original definition as well as newer uses involving such diverse subjects as organic synthesis with fluorous tags, fluorous chromatography, fluorous materials, various types of analytical measurements, and societal and sociological extensions such as 'fluorous chemists' and 'the fluorous community'. Astute readers will recognize that it also renames existing fields- fluorocarbon surfactants are now fluorous surfactants, for example. And fluorocarbon blood substitutes are now fluorous blood substitutes. (*Attention*: Teflon just became a fluorous polymer!) The word 'fluorous' is already creeping into the vocabulary of researchers in many of these established areas. Whether or not it is broadly accepted by these allied groups and circles, the liberal definition does recognize that both the established and new fields build in different ways on the same unique properties of polyfluorinated molecules or fragments.

All that glitters is not gold, and everything with fluorines is not fluorous. But where to draw the line between fluorous and non-fluorous molecules or groups? We have heard researchers call a single fluorine atom in a molecule a 'fluorous substituent'. This is way over the line. 'Fluorine' is a perfectly clear noun, and it obfuscates to replace it with a vague adjective (fluorous) modifying a vague noun (substituent). So 5-fluorouracil (5-FU) is not a fluorous molecule even though the unique properties of fluorine are in play. Perfluorohexane obviously is a fluorous molecule. In between is a vast continuum where properties and to some extent individual researchers will dictate what is or is not fluorous. (Or said another way, we do not know exactly how to define a fluorous molecule or group, but we know one when we see one.)

Within the above framework, we offer the following corollary definitions:

1. 'A *fluorous medium* is any phase of a perfluoroalkane, perfluorodialkylether, perfluorotrialkylamine, or similar non-polar species, or any similarly-composed micro-environment within a non-fluorous medium that shares key physical properties with these species'. *Fluorophilic* molecules, materials or fragments show an affinity for fluorous media under a given set of conditions, while *fluorophobic* ones do not. It is worth emphasizing that perfluoroarenes, such as hexafluorobenzene, are not fluorous under the definitions offered above. They are significantly more polar than perfluoroalkanes, and preferentially partition into organic media.
2. 'A *fluorous separation technique* is any methodology that separates fluorous or fluorous-tagged molecules from other types of molecules, or from each other, based primarily on the structure of the fluorous domain of the molecule(s)'. Fluorous separation techniques are often (but not always) based on the interactions between a fluorous medium and a fluorous portion of a molecule, and include liquid–liquid extraction with organic and fluorous solvents, and solid–liquid extraction and chromatography with fluorous solid phases. Fluorous separation techniques can also involve interaction of fluorous molecules with each other (for example, precipitation).
3. 'A *fluorous tag* (or label) is a portion or domain of a molecule that is rich in carbon-fluorine bonds and exerts primary control over the separability characteristics of the molecule in fluorous separation techniques'. There is a loose convention that a ponytail is a tag with at least six fully fluorinated carbons, stemming from the goal in much early fluorous research of compounds with very high fluorous/organic liquid partition coefficients. It is sometimes convenient to speak of 'light fluorous' and 'heavy fluorous' substances, and we suggest that the latter be reserved for cases where two or more ponytails emerge from a common atom or molecular fragment.
4. 'A *fluorous reaction component* is any participant in a reaction (catalyst, pre-catalyst, reagent, reactant/educt, product, scavenger, etc.) that is deliberately labeled with a fluorous tag'. The labeling can be permanent or temporary. This terminology also encompasses 'fluorous reaction intermediates'.
5. 'A *fluorous reaction* involves at least one fluorous reaction component, which afterwards can be separated from the non-fluorous or other fluorous components of the reaction mixture by a fluorous separation technique'.
6. '*Fluorous chemistry* is the study of the structure, composition, properties and reactions of fluorous molecules, molecular fragments, materials and media'.

We believe that the development of a consensus with respect to the above terminology, and the standardization of usage, will greatly help the continuing advancement of this field. At a less macroscopic level, there are other practices that have not yet converged to a common standard, such as units for partition coefficients (ratios vs logarithmic values) or abbreviations for ponytails and tags. Although we defer with regard to specific recommendations, we do note that IUPAC has authorized the prefix F- for perfluoro, enabling 'F-alkyl' to denote 'perfluoroalkyl' (F-surfactant = perfluorosurfactant, etc.). In any event, enhanced uniformity will certainly make it easier to attract outsiders to the field, something that benefits all members of the fluorous community.

This issue is fortunate to represent an extremely broad spectrum of this fluorous community. The classification of articles in such a far-reaching, multidisciplinary area always presents a challenge, but we have attempted to do so in the thinking that some structure is better than none—particularly for students and chemists in other disciplines. The first group of four articles features syntheses of fluorous ligands and catalysts. This is followed by three papers in which fluorous reagents and scavengers are applied to important organic reactions. These contributions, and the following sixteen dealing with a diverse spectrum of fluorous catalytic reactions, also report a variety of ligand and catalyst syntheses. Next follow five articles describing fluorous supramolecular, polymer, and materials chemistry. The subsequent group of four papers detail advances in organofluorine chemistry, and critical evaluations of two 'new' fluorous solvents. Every fluorous chemist knows that 'the most interesting stuff is at the bottom', and in this tradition the issue closes with four articles featuring fluorous bioorganic and biological chemistry. Two of these describe synthetic methodology and could have equally well been placed in earlier sections.

Where does the research collected in this issue—the first monograph-length treatment of fluorous chemistry—bring the field? One of the implicit mandates of fluorous chemists is to build a new world or ‘parallel universe’ encompassing fluorous versions of all simple monofunctional organic molecules and related building blocks, reagents, homogeneous catalysts, macromolecules, supramolecular assemblies, separation methods, etc. Some eight years after the seminal Horväth/Rabai publication, the following papers make it clear that substantial progress has been made. But in constructing this parallel universe, the many fluorous pioneers have in fact created an expanded universe, with a diverse and rapidly growing palette of unusual phenomena and exploitable properties that have no counterparts in old-world chemistry.

Since so many of these articles feature clever design elements and/or applications that could only have been dreamed about eight years ago, it is probably not too early to start dreaming about ‘fluorous life forms’, or contemplating whether the submerged mouse might be a forerunner of a modern-day ‘fluorous Frankenstein’. Regardless, each of the following papers articulates a vision, and collectively they present an outstanding opportunity to objectively and critically assess the vitality of the field. We believe that the superb chemistry described therein will prompt many readers to ‘take a dive in the fluorous pool’—no special breathing apparatus is required, the density makes it difficult to sink, and there are lots of good things swimming there.