Are Teflon "Ponytails" the Coming Fashion for Catalysts?

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Every chemist has a personal experience with separatory funnels and the liquid biphase purification of organic compounds. This well-known technique traditionally involves immiscible organic and aqueous solvents. The pH of the latter is commonly varied to extract acidic or basic by-products, and the denser phase is drawn off from the bottom of the funnel. This procedure has maintained a prominent role in preparative chemistry since the time of Berzelius nearly two centuries ago (*1*).

More recently, liquid biphase approaches to chemical reactions have attracted attention. The classic example would be "phase transfer catalysis," a phenomenon that was first recognized about 30 years ago (*2*). This technique often features an organic phase containing a lipophilic substrate and an aqueous phase containing an alkali metal salt of an anionic reagent. The latter is transported into the organic phase by a catalytic amount of a large lipophilic cation, typically a quaternary ammonium or phosphonium salt that contains one or more tentacle-like hydrocarbon chains. This methodology, furthermore, facilitates product purification. The reacted substrate commonly remains in the organic phase, whereas any new salt generated partitions into the aqueous phase.

Now a team of Exxon researchers has developed an exciting new approach to liquid biphase reactions. Horváth and Rábai (a visiting scientist from Eötvös University, Budapest) report in this issue (*3*) on "fluorous" biphase systems (FBS). These are comprised of a perfluorinated or highly fluorinated fluorous solvent and a second organic or inorganic solvent that is insoluble or poorly soluble in the former. The term fluorous, in contrast to its familiar counterpart aqueous, can be applied to a spectrum of solvents. Many are commercially available at modest cost and are generally regarded as nontoxic and biologically compatible, consistent with the extensive experience with fluorocarbon coatings in cookware and artificial organ implants over the last several decades.

Many special properties of highly fluorinated solvents, such as their ability to dissolve large quantities of oxygen, are widely recognized. However, it is perhaps less well appreciated that their miscibilities with most common organic solvents are low. Thus, either nonaqueous or aqueous biphase systems are possible. Importantly, the former allow water-sensitive reagents or catalysts to be used. Perfluorocarbon solvents have recently been used for esterifications, transesterifications, and related reactions that give small polar molecules as coproducts (*4*). These are rapidly expelled, displacing equilibria toward the target compounds. Although immiscible combinations of nonfluorinated organic solvents are known, these do not appear to have been utilized in biphase approaches to chemical reactions.

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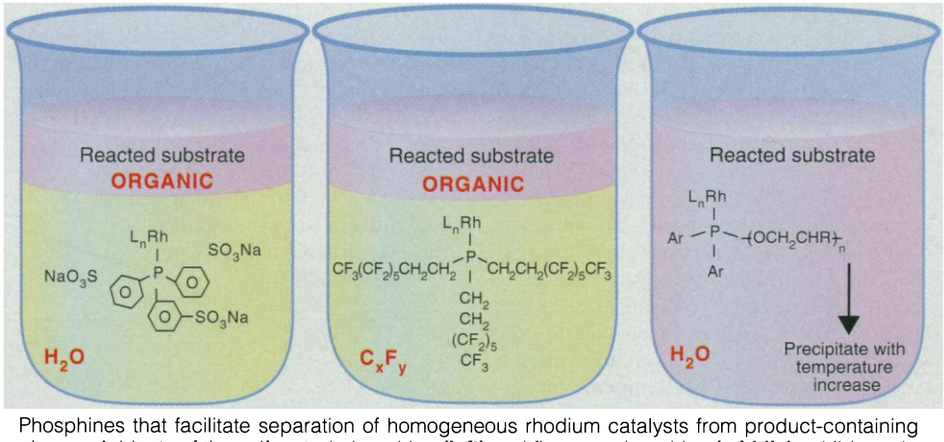

Phosphines that facilitate separation of homogeneous rhodium catalysts from product-containing phases. Adducts of the sulfonated phosphine **(left)** and fluorous phosphine **(middle)** exhibit markedly higher solubilities in aqueous and fluorocarbon phases, respectively. Alternatively, adducts of some special phosphines show decreased solubilities at lower or higher temperatures **(right)**.

Horváth and Rábai have developed an ingenious strategy for immobilizing reagents or catalysts in the fluorous phase. Namely, long carbon chains consisting mainly of perfluoroalkyl segments, descriptively termed "ponytails," are appended. These greatly increase solubility in the fluorous phase and serve as de facto anchors. In practice, several "insulating" CH_2 groups are used so that the powerful electron-withdrawing effect of the perfluoroalkyl segment is not transmitted to the reaction center. This ensures that the electronic properties of the immobilized reagent or catalyst will be close to those of the underivatized species.

Many transformations involving nonpolar reactants give products of higher polarities. These constitute particularly attractive targets for FBS chemistry, as the products should exhibit enhanced solubilities in nonfluorous phases. This design element can be found in the first application developed by Horváth and Rábai, which involves the industrially important conversion of three commodity chemicals—CO, H_2, and terminal alkenes $RCH{=}CH_2$—to aldehydes $RCH_2CH_2C(=O)H$ and their branched counterparts (alkene hydroformylation). A fluorinated phosphine with three ponytails, $[CF_3(CF_2)_5CH_2CH_2]_3P$, was initially prepared. Addition of rhodium salts gave hydroformylation catalysts containing multiple fluorinated phosphine ligands. A perfluoromethylcyclohexane-toluene biphase system was then used for the hydroformylation of 1-decene. Turnover rates were high, and the aldehyde products were easily isolated by separation of the toluene phase. Importantly, no leaching of the free phosphine or any catalytically active rhodium species from the fluorous phase was detected.

From this nascence, numerous types of applications for FBS chemistry are readily envisioned. First, in view of the high oxygen solubility in fluorous phases, there would seem to be rich potential for oxidations. Second, chiral catalysts are seeing increasing use in asymmetric organic synthesis. These are often available only by multistep syntheses, rendering them as expensive as precious metal catalysts. Immobilization in fluorous phases would facilitate recovery and reuse. Furthermore, fluorinated media are essentially untested for enantioselective reactions. The unique solvation environment might afford new or improved selectivities, or other beneficial consequences. This in turn raises an important general question for future research—namely, how do fluorous phases affect the structures and reactivities of catalytic sites? Obviously, all of the preceding concepts and issues can also be applied to immobilized stoichiometric reagents.

Horváth and Rábai also provide a dramatic dye-based visual demonstration that the miscibility of fluorous and nonfluorous phases can depend on temperature. Hence, reactions could be conducted under homogeneous conditions at elevated temperatures and then cooled to effect product separation. Other engineering advantages that could be associated with FBS chemistry are easily imagined. For example, a reaction involving a fluorinated catalyst might be conducted in a single organic phase, and a fluorous phase loop in the product stream could be used for catalyst recovery. Alternatively, in an environmental application, toxic wastes could be extracted from product streams by immobilized fluorous binding agents. It should also be kept in mind that interfacial reactions may be dominant in some FBS chemistry. As the field develops, there will be a particular need for data on this point and the effect of solvent and ponytail structure on phase properties, solubilities, and related phenomena.

The above FBS hydroformylation can also be analyzed in the context of other rhodium-catalyzed reactions involving phosphines designed to confer special phase properties. First, sulfonated aryl phosphines have been shown to similarly immobilize rhodium catalysts in the aqueous phases of organic-aqueous biphase systems. Commercial hydroformylation plants making use of this technology have been in operation since 1984 (*5*). However, rates are constrained by the limited solubilities of the reactants in the aqueous phase. Second, rhodium has also been ligated to phosphines containing poly(alkene)oxide chains, $\{CHRCH_2O\}_n$ (*6*). Such oligomeric units often give rise to water solubilities that are inversely dependent on temperature. Accordingly, the resulting hydrogenation catalyst shows an abrupt but reversible cessation of activity upon heating. This property, which has been correlated to a phase separation or precipitation of the catalyst, could have practical application as a means of controlling exotherms.

The protocol developed by Horváth and Rábai is remarkable in its conceptual elegance and insight. Its timeliness is enhanced by several parallel developments. For example, there have been significant recent advances in methodology for perfluorinating sizable, functionalized organic compounds that lack existing fluorine (*7*). There is also a rapidly growing body of data on the fundamental properties of metal complexes with perfluorinated ligands (*8*, *9*). Realistically, it does remain to be seen whether catalysts and reagents with fluorine-rich ponytails will simply be this season's fashion statement or a lasting addition to the chemist's haberdashery or trousseau. However, the strategy in this game is even easier than that in "pin the tail on the donkey," as any point of attachment can in principle produce a winner. Given the large number of industrial and academic research laboratories that will likely want to step up and play, it will be surprising if practical and widely adopted applications do not result.

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14-3-3: Modulators of Signaling Proteins?

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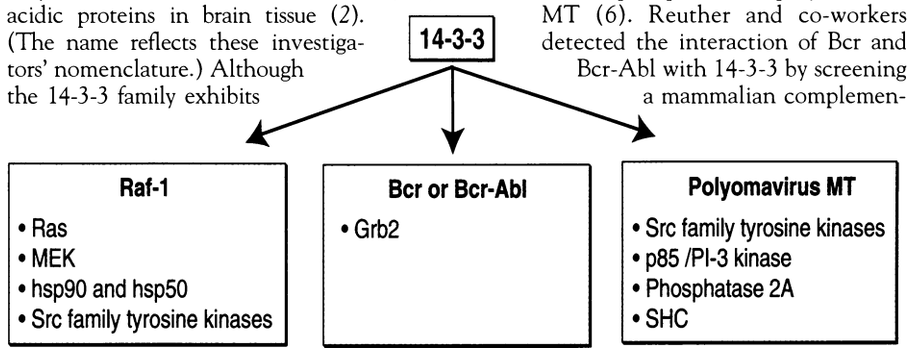
In spite of their unlikely name, the 14-3-3 proteins have been attracting attention recently. These molecules are highly conserved and are found in a broad range of organisms and tissues. At least seven mammalian isoforms of 14-3-3 have been identified, and multiple isoforms are present in most cells (*1*). 14-3-3 proteins were first identified by Moore and Perez as a series of very abundant 27- to 30-kilodalton (kD) acidic proteins in brain tissue (*2*). (The name reflects these investigators' nomenclature.) Although the 14-3-3 family exhibits a bewildering array of biological activities (*1*), many recent findings, particularly in fission yeast, point to the participation of these proteins in cell cycle control (*3*). In this issue (*4*, *5*) and in three previous reports (*6*–*8*) in *Science*, the 14-3-3 family acquires another feature of interest: Its members associate with the products of proto-oncogenes and oncogenes—in particular, Raf-1, Bcr-Abl, and the polyomavirus middle tumor antigen (MT)—suggesting that 14-3-3 proteins participate in cell transformation and mitogenic signaling pathways.



Associates of Raf-1, Bcr, Bcr-Abl, and polyomavirus MT. 14-3-3 is only one of many proteins that interact with these proto-oncogene and oncogene products.

The evidence that 14-3-3 interacts with proto-oncogene and oncogene products is compelling. 14-3-3 associates with Raf-1 in the yeast two-hybrid interaction system (*7*, *8*) and in binding assays in vitro (*4*) and is present in immunoprecipitates of Raf-1 expressed in insect cells and from mammalian cells (*4*, *8*). By protein sequencing analysis, Pallas and collaborators identified 14-3-3 in immunoprecipitates of polyomavirus MT (*6*). Reuther and co-workers detected the interaction of Bcr and Bcr-Abl with 14-3-3 by screening a mammalian complementary DNA expression library with a purified fragment of Bcr and showed that these proteins associated in vitro and coimmunoprecipitated from mammalian cells (*5*). These disparate techniques and approaches provide convincing evidence that this family of proteins indeed associates with proto-oncogene and oncogene products.

14-3-3 associates with Raf-1 at multiple sites, with the primary interaction sites located in the amino-terminal regulatory domain (*4*, *8*). The association of 14-3-3 with Raf-1, however, does not alter or interfere with the interaction of Raf-1 with Ras (*7*, *8*), which also occurs in this domain (*9*). For Bcr and Bcr-Abl, the 14-3-3 interaction site is located in the sequences encoded by

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