Facile Catalyst Separation Without Water: Fluorous Biphase Hydroformylation of Olefins

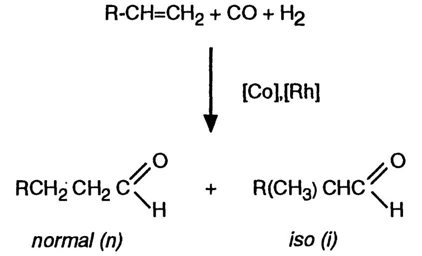
István T. Horváth* and József Rábai

A novel concept for performing stoichiometric and catalytic chemical transformations has been developed that is based on the limited miscibility of partially or fully fluorinated compounds with nonfluorinated compounds. A fluorous biphase system (FBS) consists of a fluorous phase containing a dissolved reagent or catalyst and another phase, which could be any common organic or nonorganic solvent with limited or no solubility in the fluorous phase. The fluorous phase is defined as the fluorocarbon (mostly perfluorinated alkanes, ethers, and tertiary amines)–rich phase of a biphase system. An FBS compatible reagent or catalyst contains enough fluorous moieties that it will be soluble only or preferentially in the fluorous phase. The most effective fluorous moieties are linear or branched perfluoroalkyl chains with high carbon number; they may also contain heteroatoms. The chemical transformation may occur either in the fluorous phase or at the interface of the two phases. The application of FBS has been demonstrated for the extraction of rhodium from toluene and for the hydroformylation of olefins. The ability to separate a catalyst or a reagent from the products completely at mild conditions could lead to industrial application of homogeneous catalysts or reagents and to the development of more environmentally benign processes.

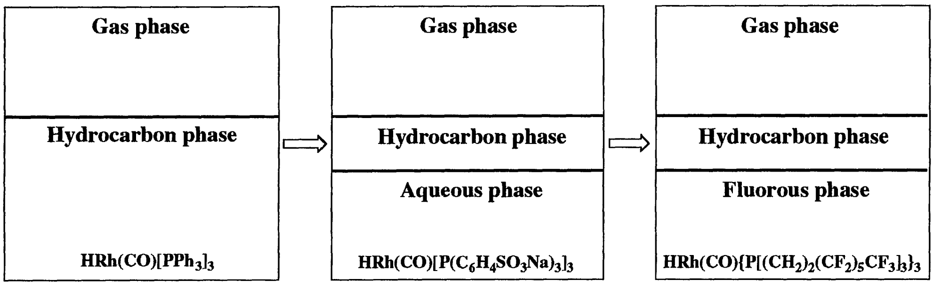
Liquid-liquid biphase systems are frequently used in synthetic, catalytic, and separation processes (1). The formation of a liquid-liquid biphase system is due to the sufficiently different intermolecular forces of two liquids resulting in limited or negligible solubility in each other. The most commonly used combinations are aqueous biphase systems, which consist of water as one phase and either hydrocarbons or other low-polarity solvents as the other. The aqueous phase may contain a dissolved reagent or catalyst (2). The use of a separate aqueous phase in chemical reactions to make products of low water solubility has the potential for easy and relatively complete recovery of the water-soluble reagents and catalysts (1, 2). Unfortunately, aqueous biphase processes cannot be used for water-sensitive chemical systems, for example, one in which a component of the system undergoes undesired chemical reactions with water. Furthermore, the low solubility of some organic substrates in water is a potential limitation of aqueous biphase reagents or catalysts.

Fluorocarbons, especially perfluorinated alkanes, ethers, and tertiary amines, are unusual because of their nonpolar nature and low intermolecular forces (3). Fluorocarbons are immiscible with water and can be used as the nonaqueous phase (4, 5). Because the solubility of O_2 in fluorocarbons is extremely high (6), fluorocarbons have been used successfully as oxygen transport media to aqueous biochemical systems (including animal lungs) (7). Surprisingly, the miscibility of perfluorinated alkanes, ethers, and tertiary amines with most common organic solvents, such as toluene, tetrahydrofuran (THF), acetone, and alcohols, is also low, and these materials form biphase systems under appropriate conditions (8). In this article, we describe the fluorous biphase system (FBS) concept for catalytic hydroformylation of olefins and its implication for chemical transformations. The term fluorous is introduced, as the analog to the term aqueous, to emphasize the fact that the chemical transformation is primarily controlled by a reagent or a catalyst designed to dissolve preferentially in the fluorous phase. The fluorous phase is defined as the fluorocarbon (mostly perfluorinated alkanes, ethers, and tertiary amines)–rich phase of a biphase system.

Fluorous biphase hydroformylation catalyst. The hydroformylation (or oxo) reaction is an important industrial process for the production of terminal (normal) aldehydes from olefins (R is an alkyl group), carbon monoxide, and hydrogen in the presence of homogeneous cobalt or rhodium catalysts (9). One of the most challenging problems associated with the triphenyl phosphine (PPh_3)–modified rhodium catalyst, such as $HRh(CO)(PPh_3)_3/PPh_3$, is the separation of higher C_n-aldehydes ($n > 8$) from the catalyst (10). The use of an aqueous biphase system, in which the water phase contains the dissolved catalyst, affords a straightforward separation of the organic products (2, 11). For example, the water-soluble $HRh(CO)[P(m\text{-}C_6H_4SO_3Na)_3]_3/[P(m\text{-}C_6H_4SO_3Na)_3]$ catalyst system has recently been developed by Rhône-Poulenc and commercialized by Ruhrchemie for the hydroformylation of propylene (11). Because the catalytic reaction occurs in the aqueous phase, the application of the aqueous biphase system is limited by the solubility of the olefins in the water phase (12). In contrast, it is expected that an FBS compatible oxo catalyst, designed to dissolve preferentially in the fluorous phase, may be used for all hydrophobic olefins because the product aldehydes have lower miscibility than the olefins in the fluorous phase (13). The evolution of the fluorous biphase hydroformylation catalyst is depicted in Scheme 1.



Because very few known phosphines (14) appeared to be compatible with the FBS concept and their synthesis seemed to be difficult, we have designed a new procedure for the preparation of $P[CH_2CH_2(CF_2)_5CF_3]_3$ (15). The role of the two methylene groups between the phosphorus atom and the perfluorohexyl moieties is to lower the electron-withdrawing effects of the perfluoroalkyl



Scheme 1

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groups (or fluorous ponytails). The phosphine was prepared by the reaction of 1*H*,1*H*,2*H*-perfluoro-1-octene with PH_3 (*16*). Although this phosphine is extremely soluble in the fluorous phase, gas chromatography (GC) and nuclear magnetic resonance (NMR) analysis of the separated hydrocarbon phases of various FBS systems showed only trace amounts of phosphine at room temperature.

The hydroformylation of 1-decene was performed with $C_6F_{11}CF_3$ as the fluorous phase and toluene as the other phase (*17*). The catalyst was prepared in situ from $Rh(CO)_2(acac)$ (acac, acetylacetonate) and $P[CH_2CH_2(CF_2)_5CF_3]_3$ (P/Rh = 40) under 75 psi (5 bar) CO/H_2(1:1). The reaction was started by charging the autoclave with 1-decene at 100°C under 150 psi (10 bar) CO/H_2(1:1) pressure, which was maintained during the reaction (Fig. 1). Upon completion of the reaction, the reactor was cooled to room temperature and depressurized. The two-phase system was separated under N_2. The upper phase was recharged to the clean autoclave. A solution of 1-octene in toluene was added under 75 psi (5 bar) CO/H_2(1:1) and heated to 100°C. The pressure was increased to 150 psi (10 bar) CO/H_2(1:1) and maintained for 24 hours. A GC analysis of the reaction mixture showed only trace amounts of 1-octene conversion. This result indicates that the FBS catalyst does not leach catalytically active rhodium species to the hydrocarbon phase under hydroformylation conditions. In contrast, when the lower fluorous phase was recharged to the autoclave, the reaction proceeded as expected to yield nonanals. These results clearly establish the facile separation of products from the catalyst as well as the ability to reuse the fluorous catalyst.

General description of the fluorous biphase concept. The FBS concept is based on the limited miscibility of partially or fully fluorinated compounds with nonfluorinated compounds (*8*). The FBS consists of a fluorous phase containing a dissolved reagent or catalyst and a second phase, which may be any organic or nonorganic solvent with limited or no solubility in the fluorous phase. The fluorous phase is defined as the fluorocarbon (all H atoms are replaced with F atoms in the parent compound)-rich or fluorohydrocarbon (at least one H atom is not replaced with F atoms in the parent compound)-rich phase of a biphase system. The most effective fluorous solvents are perfluorinated alkanes that may contain functional groups, provided there are minimal attractive interactions between those groups (*18*). It should be emphasized that perfluoroaryl groups do offer dipole-dipole interactions, making them less compatible with the FBS concept than perfluoralkyl groups. Perfluoroalkyl ethers and tertiary amines are also good candidates for the fluorous phase. An FBS reagent or catalyst is designed to preferentially dissolve in the fluorous phase, although simply having a large partition toward the fluorous phase could also be appropriate for some applications. An FBS compatible reagent or catalyst could be a fluorocarbon or fluorohydrocarbon, with or without functional groups. In the case of fluorocarbons, the presence of structural features that have attractive interactions between each other could limit the solubility in the fluorous phase and should be minimized (*18*). Furthermore, such structural features could also have attractive interactions with the constituents of the other phase, which could lead to leaching from the fluorous phase. In the case of fluorohydrocarbons, the possibilities for attractive interactions increase between the nonfluorinated parts of the molecule as well as with the constituents of the other phase.

In all of these cases, it is important to limit the attractive interactions by the use of fluorocarbon moieties. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon number that may contain other heteroatoms (the fluorocarbon tethers or fluorous ponytails). The insertion of two or three ($-CH_2-$) groups before the fluorous ponytail is necessary to decrease the strong electron-withdrawing effects of the fluorous ponytails, an important consideration if catalyst or reagent reactivity is desired to approximate that observed for the unmodified species in traditional single-phase hydrocarbon solvents. The FBS compatible reagents and ligands (for transition-metal catalysts) can be prepared by fluorination (*19*), functionalization with fluorocarbon compounds [such as the addition of fluorocarbon groups to the reagents or catalysts (*20*)], or by total synthesis.

In order to demonstrate the easy separation of the catalyst or the spent reagent from the desired reaction products, one of the most important features of FBS, a model system was assembled. The facile phase separation of a fluorous biphase system consisting of 3 ml of *n*-hexane, 1 ml of toluene, and 3 ml of perfluoromethyl-cyclohexane (*21*) at room temperature is shown in Fig. 2. The blue color of the fluorous phase is due to a perfluoroalkylated cobalt phthalocyanine complex (*22*); a similar copper phthalocyanine complex was previously developed as a "Teflon compatible" dye (*20*).

Fluorous biphase systems can be used for

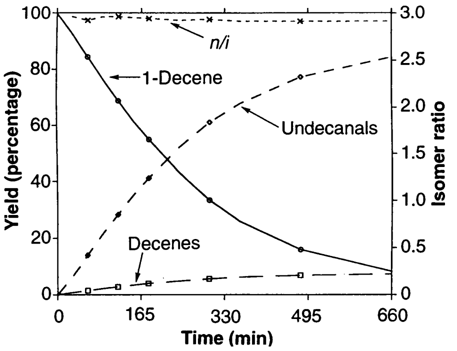


Fig. 1. The hydroformylation of 158 mmol 1-decene with 0.05 mmol $HRh(CO)\{P[CH_2CH_2(CF_2)_5CF_3]_3\}_3$ and 1.85 mmol $P[CH_2CH_2(CF_2)_5CF_3]_3$ in 35 ml of $C_6F_{11}CF_3$ and 35 ml of toluene at 150 psi (10 bar) CO/H_2(1:1) and 100°C.

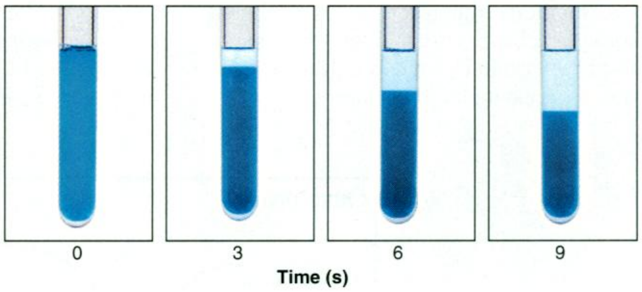


Fig. 2. Phase-separation of a *n*-hexane (3 ml)–toluene (1ml)–perfluoromethylcyclohexane (3 ml) fluorous biphase system (*21*) after shaking at room temperature. The blue color of the fluorous phase is due to a perfluoroalkylated cobalt phthanlocyanlne complex (*22*): light blue color (glass and upper phase) is due to reflection.

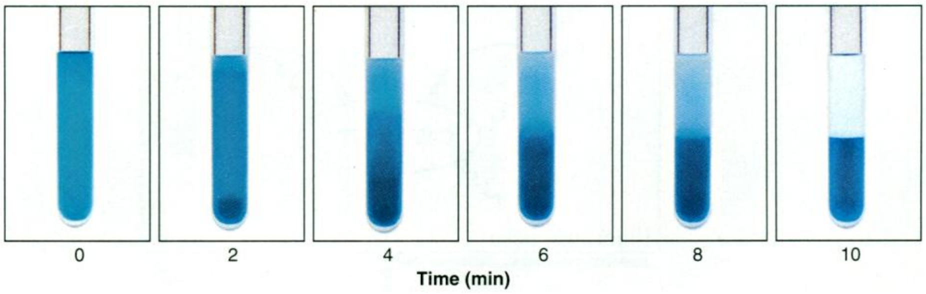
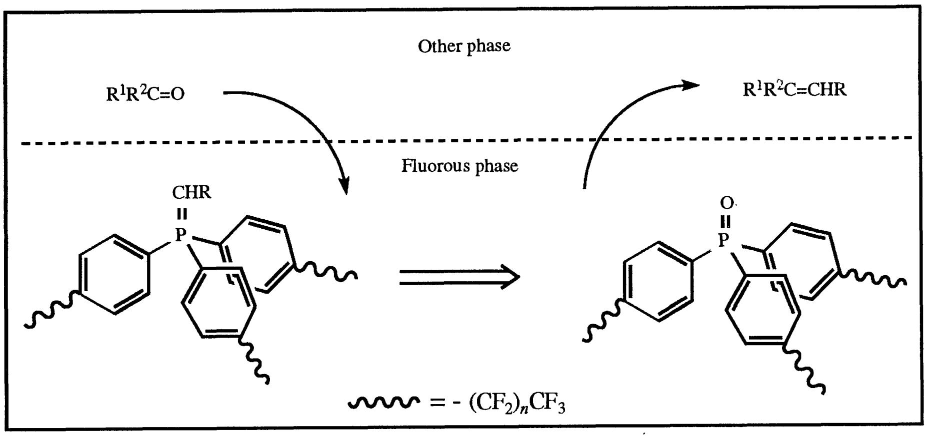


Fig. 3. Phase separation of a hand-warmed (36.5°C) *n*-hexane (3 ml)–toluene (1 ml)–perfluoromethylcyclohexane (3 ml) one-phase solution after cooling to room temperature. The blue color of the fluorous phase is due to a perfluoroalkylated cobalt phthalocyanine complex (*22*).



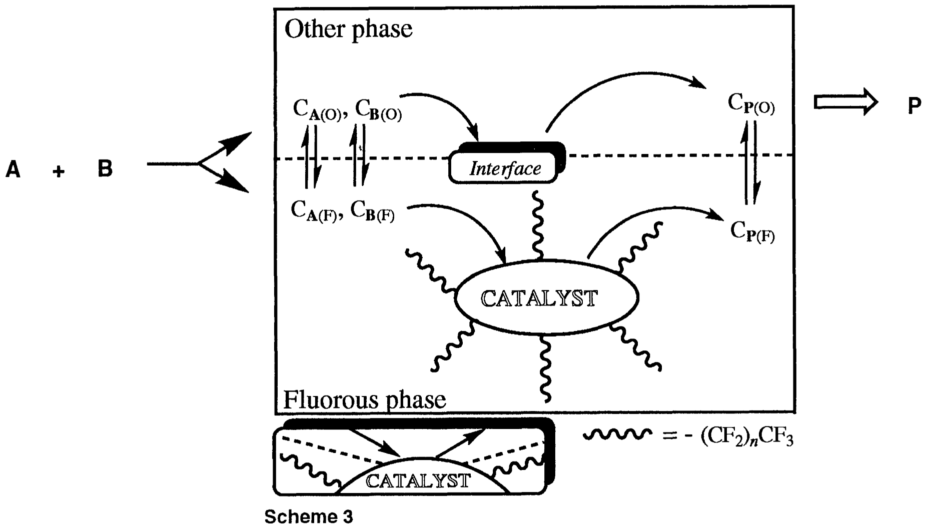
Scheme 2

both stoichiometric and catalytic reactions. We could envision the desirability of rendering a Wittig-reagent soluble in a fluorous phase by perfluoroalkyl chains (or fluorous ponytails) attached to the phenyl rings of the conventional reagent (*23*), such as $CHR=PPh_3$ (Scheme 2). The FBS concept for the catalytic conversion of reactants A and B to product P is shown in Scheme 3. The attachment of appropriate fluorous ponytails to the ligands of the homogeneous catalyst ensures that the FBS catalyst remains in the fluorous phase.

A fluorous biphase system could operate either in the fluorous phase or at the interface of the two phases, depending on the solubilities of the reactants in the fluorous phase. When the solubilities of the reactants are very low in the fluorous phase, the chemical reaction can still occur at the interface (see insert in Scheme 3) or appropriate phase transfer agents (*1*) may be added to facilitate the reaction. Note that a fluorous biphase system could become a one-phase system by increasing the temperature. For example, the fluorous biphase system consisting of 3 ml of *n*-hexane, 1 ml of toluene, and 3 ml of perfluoromethylcyclohexane (*21*) becomes a one-phase system at 36.5°C (Fig. 3). The ability to operate in a one-phase mode could be important when mass transfer from the nonfluorous phase to the fluorous phase is rate limiting. Finally, the peculiar physical properties of a fluorous phase could lead to unexpected solvent effects, including significantly altered reactivities or selectivities or both (*24*).

Fluorous biphase extraction. The application of FBS for the extraction of rhodium from a hydrocarbon phase with fluorous soluble ligands is a novel approach to heavy-metal recovery, an extremely important area of environmental chemistry. Rhodium is one of the most expensive transition metals used in many homogeneous catalytic processes, and the chemistry of rhodium phosphine complexes is well established (*25*). We have studied the extraction of rhodium from toluene with an FBS-compatible phosphine. The extraction of rhodium proceeds smoothly when a solution of $Rh(CO)_2(acac)$ in toluene is shaken with a solution of $P[CH_2CH_2(CF_2)_5CF_3]_3$ (P/Rh = 6) in $C_6F_{11}CF_3$ at room temperature for a few minutes (*26*). Treatment of the fluorous phase with 150 psi (10 bar) CO/H_2 at 70°C resulted in the formation of $HRh(CO)\{P[CH_2CH_2(CF_2)_5CF_3]_3\}_3$ (*27*).

Catalytic and synthetic opportunities. We have established that FBS is a viable approach for effecting chemical transformations in the fluorous phase. The ability to completely separate a catalyst or a reagent from the products at mild conditions could expand the application of homogeneous catalysts or reagents in industrial processes. In addition, it could lead to the design and synthesis of novel catalysts and reagents with extremely high selectivity. One important rule for such design is that the reagents or catalysts have to be fluorous like, because it has been known for centuries that "*similia similibus solvuntur*," or "like dissolves like" (*24*). Although new reagents and catalysts could be designed to adopt to the fluorous environment, many "hydrocarbonlike" reagents or catalysts could be converted to "fluorouslike" ones by the incorporation of fluorous ponytails of appropriate number, size, and shape. It should be reemphasized that the insertion of two or three ($-CH_2-$) groups before the fluorous ponytail is necessary to decrease the strong electron-withdrawing effects of the fluorous ponytails. Although it is hard to predict the most attractive applications of FBS at such an early stage, fluorous extraction of poisonous metals from water or hydrocarbons or both seems a challenging new direction for environmental chemistry. The development of fluorous reagents and catalysts for selective functionalization of organic molecules could be another fruitful area for FBS. Finally, chiral fluorous reagents and catalysts for asymmetric transformations could offer a new avenue in the affordable synthesis of biologically important molecules.



Scheme 3

REFERENCES AND NOTES

1. W. P. Weber and G. W. Gokel, *Phase Transfer Catalysis in Organic Synthesis* (Springer-Verlag, New York, 1977); R. W. Rousseau, *Handbook of Separation Process Technology* (Wiley, New York, 1987).
2. F. Joó and Z. Tóth, *J. Mol. Cat.* **8**, 369 (1980); W. A. Herrmann and C. W. Kohlpaintner, *Angew. Chem. Int. Ed. Engl.* **32**, 1524 (1993).
3. A. V. Grosse and G. H. Cady, *Ind. Eng. Chem.* **39**, 367 (1947); C. W. Bunn and E. R. Howells, *Nature* **174**, 549 (1954); R. L. Scott, *J. Phys. Chem.* **62**, 136 (1958).
4. R. D. S. Stevens and P. M. Brown, U.S. Patent 4,793,931 (1988).
5. Y. Sato, Jpn. Kokai Tokkyo Koho, JP 04 01, 174 (1992).
6. W. F. Linke, *Solubilities* (American Chemical Society, Washington, DC, 1965), vol. 2, p. 1236; J. G. Riess and M. Le Blanc, *Pure Appl. Chem.* **54**, 2383 (1982).
7. L. C. Clark Jr. and F. Gollan, *Science* **152**, 1755 (1966); T. H. Maugh II, *ibid.* **206**, 205 (1979).
8. R. L. Scott, *J. Am. Chem. Soc.* **70**, 4090 (1948); J. H. Hildebrand and D. R. F. Cochran, *ibid.* **71**, 22 (1949);

N. M. Zadymova, Z. N. Markina, N. K. Evseeva, E. D. Shchukin, *Kolloidn. Zh.* **50**, 825 (1988); D. L. Dorset, *Macromolecules* **23**, 894 (1990); J. Kloubek, *Colloids Surf.* **55**, 191 (1991); D. W. Zhu, *Synthesis* **1993**, 953 (1993).

9. J. Falbe, *New Syntheses with Carbon Monoxide* (Springer-Verlag, Berlin, 1980).
10. J. D. Jamerson, R. L. Pruett, E. Billig, R. A. Fiato, *J. Organomet. Chem.* **193**, C43 (1980).
11. E. G. Kuntz, *Chemtech* **17**, 570 (1987); E. Wiebus and B. Cornils, *Chem. Ing. Tech.* **66**, 916 (1994).
12. I. T. Horváth, *Catal. Lett.* **6**, 43 (1990).
13. Separation of an *oxo* FBS system consisting of 3 ml of a mixture of 1-decene (20 percent) and 1-undecanal (80 percent) and 3 ml $C_6F_{11}CF_3$ at 40°C: upper phase, 2.7 percent $C_6F_{11}CF_3$, 19.5 percent 1-decene, and 77.8 percent 1-undecanal; lower phase, 99.3 percent $C_6F_{11}CF_3$, 0.7 percent 1-decene, and trace amounts of 1-undecanal.
14. C. Tamborski, C. E. Snyder Jr., J. B. Christian, U.S. Patent 4,454,349 (1984); H. Gopal, C. E. Snyder Jr., C. Tamborski, *J. Fluorine Chem.* **14**, 511 (1979), and references therein.
15. S. Benefice-Malouet, H. Blancou, A. Commeyras, *J. Fluorine Chem.* **30**, 171 (1985).
16. A 100-ml glass-lined autoclave was charged under N_2 with 35 g (100 mmol) 1*H*,1*H*,2*H*-perfluoro-1-octene, 0.6 g azobis(isobutyronitrile), and 0.85 g (25 mmol) PH_3 at room temperature. The mixture was stirred and heated to 100°C and kept at that temperature for 2 hours. After the reactor was cooled to room temperature, the unreacted PH_3 was vented to a scrubber containing 37 percent aqueous formaldehyde solution and 0.05 percent $RhCl_3$. Analysis by GC and ^{31}P NMR (in CF_2ClCCl_2F) showed the formation of $H_2PCH_2CH_2(CF_2)_5CF_3$ (2 percent, −139.3 ppm, t, coupling constant J_{P-H} = 189 Hz), $HP[CH_2CH_2(CF_2)_5CF_3]_2$ (4 percent, −67.1 ppm, d, J_{P-H} = 194 Hz), and $P[CH_2CH_2(CF_2)_5CF_3]_3$ (20 percent, −24.9 ppm). Addition of azobis(isobutyronitrile) (0.25 g) and heating the solution at 80°C for 8 hours resulted in the disappearance of the mono- and dialkylphosphines. The reaction mixture was diluted with 25 ml of C_6F_{14} and washed with toluene (four times with 15 ml). Distillation under vacuum (155°C at 0.3 torr) yielded 26 percent tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)phosphine.
17. A mixture of 0.05 mmol $Rh(CO)_2(CH_3COCHCOCH_3)$ in 35 ml of toluene and 2.00 mmol $P[CH_2CH_2(CF_2)_5CF_3]_3$ in 35 ml of $C_6F_{11}CF_3$ was charged to a 300-ml autoclave under 75 psi (5 atm) CO/H_2(1:1) and heated to 100°C. A 75-ml pressure bomb was charged with 158 mmol 1-decene and attached to the autoclave. When the temperature in the autoclave reached 100°C, the 1-decene was added by using 150 psi (10 atm) CO/H_2(1:1) pressure, which was maintained during the reaction. After the reaction was complete, the reactor was cooled to room temperature. The autoclave was depressurized, and the two-phase system was separated in a separatory funnel under N_2. The ^{31}P NMR and GC analysis of the spent fluorous phase revealed that the phosphine ligand remained unchanged during the reaction. The upper phase was recharged to the cleaned and catalytically inactive autoclave. A solution of 30 ml of 1-octene in 35 ml of toluene was added under 75 psi (5 bar) CO/H_2(1:1) and heated to 100°C. The pressure was increased to 150 psi (10 bar) CO/H_2(1:1) and maintained for 24 hours. A GC analysis of the reaction mixture showed only trace amounts of conversion of 1-octene. In contrast, when the lower phase was charged to the autoclave, the hydroformylation of 1-octene proceeded to give 85 percent nonanals with *n*/*i* ratio of 2.9 and 8 percent octenes.
18. J. F. Liebman, A. Greenberg, W. R. Dolbier Jr., *Fluorine-Containing Molecules. Structure, Reactivity, Synthesis, and Applications* (VCH Press, New York, 1988).
19. M. Hudlicky, *Chemistry of Organic Fluorine Compounds* (Macmillan, New York, 1962).
20. Minnesota Mining and Manufacturing Co., British Patent 840,725 (1960).
21. Upper phase, 12.5 percent C_7F_{14}, 51.3 percent *n*-hexane, 36.2 percent toluene; lower phase, 58.7 percent C_7F_{14}, 27.2 percent *n*-hexane, 14.1 percent toluene.
22. A heavy-wall Pyrex tube containing a mixture of 0.5 mmol of phthalocyaninato cobalt(II) and 5 mmol of perfluorodecyl iodide under argon was heated in a heat bath at 250°C for 12 hours, and the temperature was increased to 290°C in 2 hours. After the tube was cooled to room temperature, the crude reaction product was extracted with 40 ml of perfluorohexane. The solvent was removed in vacuo at room temperature, and all of the volatile side products were removed by high vacuum at 100°C.
23. J. March, *Advanced Organic Chemistry* (Wiley, New York, 1992), pp. 956–963.
24. C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry* (VCH Press, Weinheim, 1990).
25. R. S. Dickson, *Hydrogen and Carbon Compounds of Rhodium and Iridium* (Reidel, Amsterdam, 1985).
26. A solution of 0.3 mmol $P[CH_2CH_2(CF_2)_5CF_3]_3$ in 35 ml of $C_6F_{11}CF_3$ was mixed with a light yellow solution of 12.9 mg (0.05 mmol) $Rh(CO)_2(acac)$ in 35 ml of toluene under argon. The resulting two-phase system contained a colorless upper phase and a slightly yellow lower phase, indicating the transfer of the rhodium from the toluene phase to the fluorous phase.
27. NMR data for $HRh(CO)\{P[CH_2CH_2(CF_2)_5CF_3]_3\}_3$ in $C_6F_{11}CF_3$: ^1H NMR: $\delta = -11.82$ ppm (J_{P-H} = 19 Hz and J_{H-C} = 35 Hz), ^{31}P NMR: $\delta = 21.2$ ppm (J_{P-Rh} = 148 Hz and J_{P-C} = 10 Hz).
28. The careful technical work of R. A. Cook and K. A. Eriksen is gratefully acknowledged. We are indebted to R. L. Espino, P. J. Guzi, A. Kaldor, M. G. Matturro, S. C. Mraw, P. S. Stevens, and W. Weissman for their support and encouragement.

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Crystal and Molecular Structure of a Collagen-Like Peptide at 1.9 Å Resolution

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The structure of a protein triple helix has been determined at 1.9 angstrom resolution by x-ray crystallographic studies of a collagen-like peptide containing a single substitution of the consensus sequence. This peptide adopts a triple-helical structure that confirms the basic features determined from fiber diffraction studies on collagen: supercoiling of polyproline II helices and interchain hydrogen bonding that follows the model II of Rich and Crick. In addition, the structure provides new information concerning the nature of this protein fold. Each triple helix is surrounded by a cylinder of hydration, with an extensive hydrogen bonding network between water molecules and peptide acceptor groups. Hydroxyproline residues have a critical role in this water network. The interaxial spacing of triple helices in the crystal is similar to that in collagen fibrils, and the water networks linking adjacent triple helices in the crystal structure are likely to be present in connective tissues. The breaking of the repeating $(X\text{-}Y\text{-}Gly)_n$ pattern by a Gly→Ala substitution results in a subtle alteration of the conformation, with a local untwisting of the triple helix. At the substitution site, direct interchain hydrogen bonds are replaced with interstitial water bridges between the peptide groups. Similar conformational changes may occur in Gly→X mutated collagens responsible for the diseases osteogenesis imperfecta, chondrodysplasias, and Ehlers-Danlos syndrome IV.

Until now, the triple helix was the only major regular protein motif that had not been elucidated by single crystal x-ray diffraction. The triple helix is characteristic of collagen proteins, and it also appears as a structural element in some proteins with host defense functions, such as the macrophage scavenger receptor (*1*) and C1q (*2*). The first models for the molecular conformation of collagen were proposed in the mid-1950s (*3–6*) on the basis of the unusual amino acid features of collagen and the high angle x-ray fiber diffraction pattern of tendon. The currently accepted model (*5*, *7*) consists of three polypeptide chains, each in an extended, left-handed polyproline II–like helix, which are staggered by one residue and then supercoiled about a common axis in a right-handed manner. Interchain hydrogen bonds between C=O and N–H groups stabilize the structure.

Triple helix sequence constraints are strict. Close-packing of the chains near the central axis imposes the requirement that glycine occupy every third position, generating an $(X\text{-}Y\text{-}Gly)_n$ repeating sequence. Proline and 4-hydroxyproline, which in collagens constitute about 20 percent of all residues, are found almost exclusively in the

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