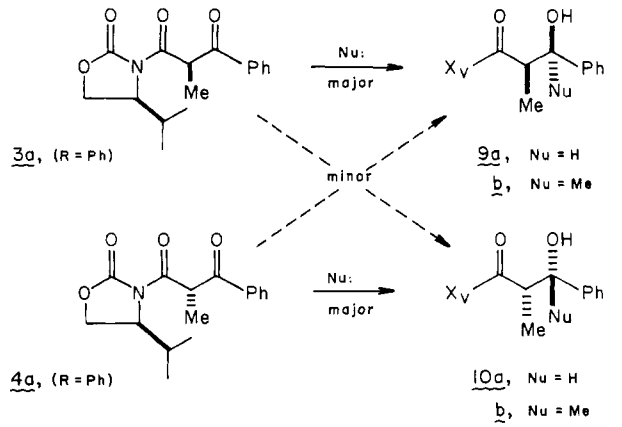
Scheme II



between either propionyl or methyl substituents and the imide nitrogen substituents associated with the chiral auxiliary.[13] Stated in an alternative manner, the above-mentioned steric effects appear to attenuate the influence of the exocyclic imidic carbonyl toward H_α acidification by the destabilization of that conformation aligning H_α and the carbonyl π-system.

The aforementioned observations relative to the stability of these β-keto imide systems suggests that selective chemical modification of these substrates is feasible. For example, we have found that the highly diastereoselective carbonyl addition reactions illustrated in Scheme II are possible. Reduction of the β-keto imide **3a** (R = Ph) with zinc borohydride (0.02 M substrate in CH_2Cl_2 to which was added 1 molar equiv 0.24 M of $Zn(BH_4)_2$ in ether; 0 °C, 30 min) afforded >100:1 of the β-hydroxy imide **9a** in >95% yield. The analogous reduction of the diastereomeric β-keto imide **4a** (R = Ph) proceeded in quantitative yield with the same level of diastereoselection to afford **10a**. Identical results were obtained in the related reductions of **3a** and **4a** (R = Et), **3b** and **4b** (R = Ph), and **3b** and **4b** (R = Et). In contrast, sodium borohydride was observed to be nonstereoselective with these substrates. These results establish the fact that the proximal, methyl-bearing stereocenter is solely responsible for the observed 1,2-asymmetric induction and that metal ion chelation is a crucial factor in diastereoface selection.[14] More significantly, it has been found that the addition of **3a** and **4a** (R = Ph) (0.2 M in CH_2Cl_2) to a ethereal solution of 3 equiv of methylmagnesium bromide (1.0 M solution in 1:2 Et_2O:CH_2Cl_2, -78 °C, 4 h). cleanly afforded the adducts **9b** and **10b**, respectively, in >90% yield.

In summary, prior to this study, the efficient construction of chiral β-dicarbonyl synthons had not been directly accessible.[15] The direct acylation of these chiral imide enolates now provides a direct entry into this potentially useful class of chiral synthons. More complex applications of this methodology are currently under investigation.

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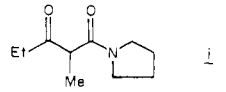
(13) This argument suggests that *N,N*-dialkylamides derived from α-substituted β-keto acids should also exhibit related low kinetic acidities. This is apparent from the one case that we have examined. Amide i exhibited no



i

discernable enol content by ^1H NMR ($CDCl_3$) and no detectable H-D exchange in pyridine-CD_3OD (25 °C, 3 days).

(14) For related reductions, see: (a) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641. (b) Nakata, T.; Kuwabara, T.; Tani, Y.; Oishi, T. *Ibid.* **1982**, *23*, 1015. (c) DiPardo, R. M.; Bock, M. G. *Ibid.* **1983**, *24*, 4805.

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Functional Fluorocarbon Micelles. Specific Rate Enhancement in the Catalytic Hydrolysis of Phenyl Esters due to Selective Binding of Fluorocarbon and Hydrocarbon Substrates

T. Kunitake,* H. Ihara, and Y. Hashiguchi

Contribution No. 667, Department of Organic Synthesis Faculty of Engineering, Kyushu University Fukuoka 812, Japan

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Micelles of perfluoroalkyl surfactants have attracted increasing attention in recent years, because of their peculiar physicochemical characteristics compared with those of the hydrocarbon counterparts. Generally speaking, fluorocarbon surfactants give much reduced surface tension[1] and show limited miscibility with hydrocarbon micelles.[2-6] In spite of these peculiarities, their use as functional micelles has, to the best of our knowledge, not been examined.

The present study was initiated on the basis of our presumption that high efficiency and novel selectivity in catalysis are attainable by making use of the peculiar characteristics of fluorocarbon micelles. The catalytic action of cationic hydrocarbon micelles has been extensively investigated especially in the hydrolysis of phenyl esters.[7,8] Therefore, it is interesting to compare the catalytic action by cationic fluorocarbon micelles toward fluorocarbon and hydrocarbon substrates. The structures of catalyst and substrate used in this study and their abbreviations are shown in Chart I.[9]

Zwitterionic long-chain (hydrocarbon) hydroxamates provide efficient, micellar nucleophiles without additional surfactants, and their catalytic behavior in the hydrolysis of hydrocarbon phenyl esters has been examined.[11] We chose the same type of nucleophile in this study. The long-chain moiety is, however, fluorocarbon. The substrates are *p*-nitrophenyl esters, and the acyl portion is either a long-chain fluorocarbon or a hydrocarbon. PNPA is also used as reference.

The catalytic hydrolysis was carried out as follows. A stock solution of the catalyst, which was prepared by sonication (Bransonic Cell Disruptor, 185), was added to a borate buffer solution, and the mixture (3000 μL) was kept at 30 °C in a UV cell. The reaction was initiated by adding 10 μL of substrate in acetonirile (< 0.5 vol % of the reaction mixture), and the rate of hydrolysis was estimated by appearance of *p*-nitrophenolate (400 nm). The catalyst was always used in excess, and the pseudo-first-order rate law was satisfied up to at least 80% of reaction. The spontaneous rate (alkaline hydrolysis) was negligibly small. The extent of dissociation of the hydroxamic acid unit (α) was determined by UV titration of the hydroxamate anion (240 nm).[11,12]

Figure 1 describes the dependence of the pseudo-first-order rate constant for the hydroxamate anion, k_1 ($=k_{obsd}/\alpha$), on the catalyst concentration. Because of the large rate difference, a low medium pH (6.3) was selected for the combination of C^F_{10}-HA-C_4N^+ and C^F_{10}-PNP, and a higher pH (7.6) was used for the other systems. The C^F_{10}-PNP substrate hydrolyzed with remarkable efficiency, and the rate saturation is complete in the presence of ca. 20 equiv

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Table I. Catalytic Hydrolysis by Fluorocarbon and Hydrocarbon Amphiphiles[a]

	catalyst					
	C^F_{10}-HA-C_4N^+			$2C_{18}$-HA-C_4N^+		
substrate	C^F_{10}-PNP	C_{12}-PNP	PNPA	C^F_{10}-PNP	C_{12}-PNP	PNPA
10^2k_1, s^{-1}	185	8.4	0.45	0.11	12	0.71
relative k_1	1700	76	4	1	110	6

[a] 30 °C, 0.02 M borate buffer, μ = 0.01 (KCl), [catalyst] = 1.0×10^{-4} M, [substrate] = 1.0×10^{-5} M.

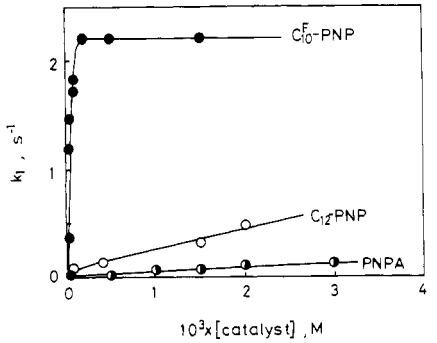
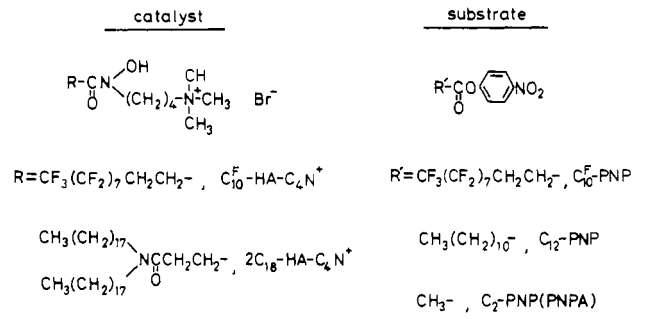


Figure 1. Catalytic hydrolysis of phenyl esters: 30 °C, 0.02 M borate buffer, μ = 0.05 (KCl), catalyst C^F_{10}-HA-C_4N^+, substrates 1.0×10^{-5} M.

Chart I



of C^F_{10}-HA-C_4N^+. The reaction of the hydrocarbon substrates, C_{12}-PNP and PNPA, proceeds less efficiently and without rate saturation.

The k_1 values at a catalyst concentration of 1.0×10^{-4} M are compared in Table I. The data obtained with the corresponding hydrocarbon (bilayer) catalyst, $2C_{18}$-HA-C_4N^+, are also included.[13] It is immediately apparent that both catalysts show analogous reactivities toward PNPA. This implies that the PNPA substrate is not strongly (or not deeply) bound to these catalytic aggregates, as expected from its lessened hydrophobicity. In the absence of strong binding, the difference in the long-chain portion (hydrocarbon vs. fluorocarbon) of the catalyst would not be influential in the reaction. In contrast, the catalytic reactivities toward C^F_{10}-PNP are very different; the fluorocarbon catalyst being 1700 times more efficient than the hydrocarbon catalyst. The saturation kinetics shown in Figure 1 strongly indicate that this remarkable rate difference arises from much enhanced binding of the fluorocarbon substrate to the fluorocarbon catalyst.

Interestingly, in the case of the C_{12}-PNP substrate, the two catalysts gave relatively large efficiencies of similar magnitude. This result appears strange, if the selective binding of hydrocarbon and fluorocarbon components produces a large rate difference as discussed above. It must be noted, however, that the hydrophobic portion of the fluorocarbon catalyst is made of hydrocarbon ($-C_4H_8-$) and fluorocarbon ($C_8F_{17}-$) components. C_{12}-PNP is probably bound to the hydrocarbon region of the fluorocarbon micelle.

In conclusion it is established that enhanced selectivities in catalysis can be created by a combination of micellar rate enhancements and discriminatory binding of hydrocarbon and fluorocarbon components.

(13) The reactivity of $2C_{18}$-HA-C_4N^+ is close to those of single-chain (hydrocarbon) zwitterionic hydroxamate.[11] Therefore, it appears that the aggregate morphology (micelle vs. bilayer) does not exert a significant influence on the hydroxamate reactivity. An attempt to synthesize a single-chain hydroxamate corresponding to $2C_{18}$-HA-C_4N^+ failed, because the final product obtained upon debenzylation lost its hydroxamate activity quickly when dissolved in water.

Conformational Origin of the Nonequivalent ^{13}C NMR Chemical Shifts Observed for the Isopropyl Methyl Carbons in Branched Alkanes

A. E. Tonelli,* F. C. Schilling, and F. A. Bovey

AT&T-Bell Laboratories
Murray Hill, New Jersey 07974

Received September 12, 1983

Over 25 years ago, Drysdale and Phillips[1] observed geminal nonequivalence of ^{19}F nuclei in acyclic compounds by NMR. Nair and Roberts[2] confirmed these results and rationalized them in terms of conformational preference. Shoolery and Crawford[3] observed a corresponding nonequivalence of ^{19}F scalar couplings. Waugh and Cotton[4] noted that even in the absence of a conformational preference the geminal nonequivalence would still persist. Gutowsky[5] considered this latter aspect in greater detail. More recently van Gorkom and Hall[6] and Jennings[7] have reviewed the chemical shift nonequivalence of geminal groups in NMR spectra.

In the present paper we consider the ^{13}C NMR nonequivalence of the methyl carbons belonging to an isopropyl group attached to branched alkanes. Roberts and co-workers,[8] Lindeman and Adams,[9] and Carman and co-workers[10] have reported differences in ^{13}C NMR chemical shifts for methyl carbons in terminal isopropyl groups. Table I lists the branched alkanes studied by these investigators and presents the geminal nonequivalence observed by them. As discussed in the review by Jennings,[7] each of the compounds exhibiting geminal nonequivalence falls in either of two classes. They are either chiral or, if achiral, lack a plane of symmetry that bisects the CH_3–CH–CH_3 angle of the isopropyl group.

We have calculated the ^{13}C NMR chemical shift difference expected for the isopropyl methyl carbons in all but one of the branched alkanes listed in Table I. The γ-gauche effect method, which we previously demonstrated[11] can be utilized to predict the stereosequence-dependent ^{13}C NMR chemical shifts in vinyl homo- and copolymers and their model compounds, was used to calculate the methyl carbon chemical shifts.

As an illustration, consider 2,4-dimethylhexane (2,4-DMH), shown in Figure 1. The isopropyl methyl carbons, arbitrarily designated as side-chain (sc) and backbone (bb), are shielded[11] by their gauche arrangements with their γ substituent, the asymmetric C_4 methine carbon. The probabilities for these gauche

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