2-Formyl-4-pyrrolidinopyridine (FPP): A New Catalyst for the Hydroxyl-Directed Methanolysis of Esters

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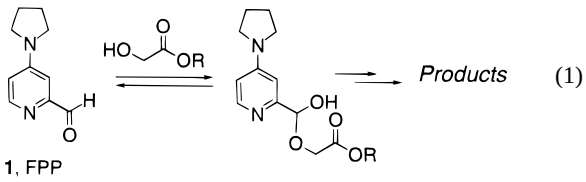
Catalysts for the acylation of alcohols with active esters are well known and widely used.[1] Species such as 4-pyrrolidinopyridine (PPY) or 4-(dimethylamino)pyridine (DMAP)[2] can display remarkable enhancements in the rate of acylation of a variety of alcohols under mild conditions. However, catalysts that are capable of the selective hydrolysis of one ester in the presence of another are less common.[3,4] We describe in this communication a derivative of PPY, 2-formyl-4-pyrrolidinopyridine (FPP, **1**), which is a selective catalyst for the hydroxyl-directed[5] methanolysis of hydroxy esters and which operates by a novel mechanism.

FPP is unique in that it contains a basic component (a 4-aminopyridine) in conjugation with a deactivating electrophilic component (an aldehyde, eq 1). The 4-aminopyridine nucleus



(1)

1, FPP

is known to be a very active system for acyl transfer catalysis.[2] Our interest in the preparation of a selective catalyst led us to consider attenuating the activity of this species toward ordinary active esters while maintaining its activity toward hydroxy esters. Attenuation can be accomplished by substituting the pyridine with an electron-withdrawing group, thereby diminishing the basicity and nucleophilicity of the pyridine nitrogen. We chose to use an aldehyde for this purpose because of its electron-withdrawing character and because of its ability to reversibly bind to the alcohol of a hydroxy ester with concomitant formation of a hemiacetal (eq 1). This binding serves two important functions; it brings the ester in close proximity to the pyridine nitrogen (induced approximation),[6] and it activates the catalyst once the alcohol is bound by converting the electron-withdrawing aldehyde to a hemiacetal which is not as electron-withdrawing.[7] This activation of the pyridine upon binding is crucial for selectivity because it ensures that substrates that do not bear a hydroxyl group will encounter a less active catalyst, thereby slowing the rate of non-hydroxyl-directed background hydrolysis.[8]

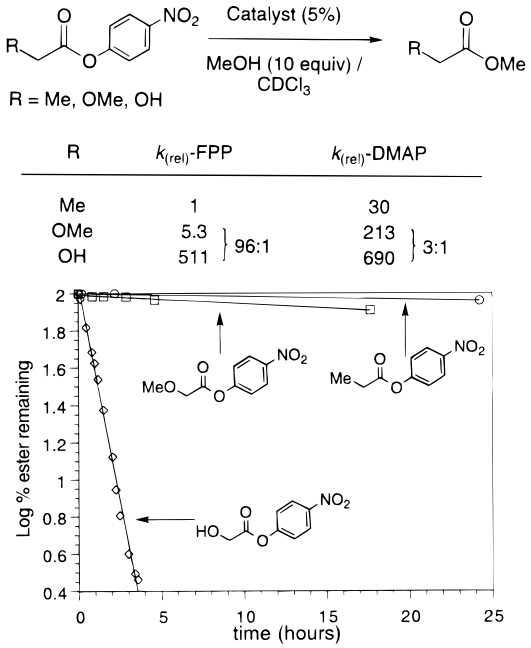


Figure 1. Graph of selective hydrolysis using 5% FPP.

We first compared the reactivity of FPP with DMAP in the acylation of menthol using acetic anhydride and 2% catalyst in the absence of triethylamine. Under these conditions, the DMAP-catalyzed reaction is about 300 times faster than the FPP-catalyzed reaction.[9] In fact, we observed no increase in the rate of acylation using FPP as compared to a control containing no catalyst. The reactivity of these two catalysts was then compared in the methanolysis of the *p*-nitrophenyl (PNP) ester of glycolic acid in $CDCl_3$ (10 equiv of methanol, 5 mol % catalyst, 0.1 M substrate at 20 °C). With this substrate, which is an α-hydroxy ester, DMAP and FPP displayed very similar reactivities (k_{rel}(DMAP/FPP) = 690/511 = 1.35, Figure 1).[10,11] To further probe the selectivity of FPP, we compared the rate of methanolysis of the PNP esters of propionic acid, methoxyacetic acid, and glycolic acid with DMAP and with FPP (5 mol %) in $CDCl_3$ containing 10 equiv of methanol (Figure 1). As expected due to electronic and hydrogen-bonding

(1) For a review on methods of synthesis of esters, see: (a) Mulzer, J. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 2.2. For recent examples of nucleophilic catalysts, see: (b) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (c) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. *J. Org. Chem.* **1993**, *58*, 7286. (d) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (e) Menger, F. M.; Whitesell, L. G. *J. Am. Chem. Soc.* **1985**, *107*, 707.

(2) (a) Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981. Reviews: (b) Cherkasova, E. M.; Bogatkov, S. V.; Golovina, Z. P. *Russ. Chem. Rev.* **1977**, *46*, 246;. (c) Hofle, G.; Steglich, V.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (d) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

(3) Enzymes are sensitive to the structure of an ester and will hydrolyze similar esters with exquisite selectivity. They are not, however, as general in their scope as man-made catalysts. For reviews on the use of acyl transfer enzymes in organic synthesis, see: Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; Chapter 2. Sih, C. J. *Top. Stereochem.* **1989**, *19*, 63. Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. Haraldsson, G. G. The Application of Lipases in Organic Synthesis. In *The Chemistry of the Functional Groups, Suppl. B, The Chemistry of Acid Derivatives*; Patai, S., Ed.; John Wiley and Sons: Chichester, 1992; Vol. 2.

(4) Evans has applied Weinreb's transamination method (Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989) to his acyl oxazolidinone reagents and found that a β-hydroxyl or an α-heteroatom is required in order to avoid attack at the oxazolidinone carbonyl. See: Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799.

(5) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(6) For a discussion, see: Jencks, W. P. *Catalysis in Chemistry and Enzymology*; Dover: New York, 1986: pp 31−40.

(7) This is a variation of Sharpless's concept of ligand-accelerated catalysis with the exception that the ligand is the substrate for the reaction. For a review in this area, see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

(8) This catalyst is used in the presence of methanol, and while it is true that the addition of methanol to the aldehyde of the catalyst produces a hemiacetal, this species is sterically deactivated.

(9) In the presence of triethylamine, the DMAP-catalyzed reaction is too fast to conveniently monitor by GC. We note that the acetic acid that is produced as a byproduct is known to inhibit the activity of DMAP if no other base is present. This value therefore represents a lower limit on the relative rates of the DMAP- versus the FPP-catalyzed reaction.

(10) All relative rates reported were determined under identical conditions and are normalized to the slowest reaction.

(11) The rates of methanolysis of the PNP ester of glycolic acid using DMAP and PPY are comparable.

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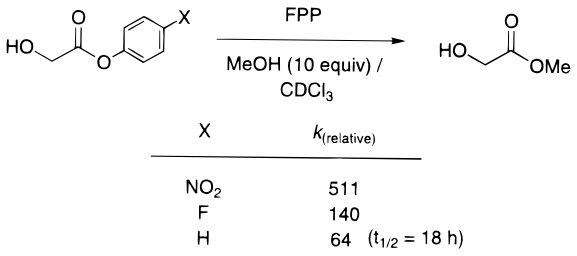


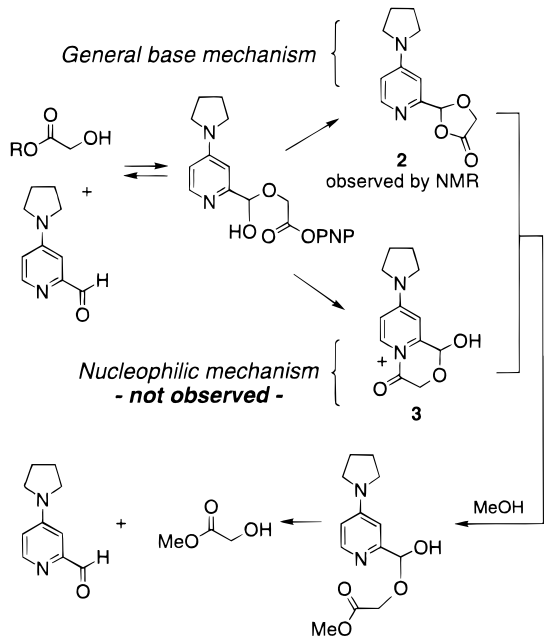
Figure 2.

effects, the alkoxy- and hydroxy-substituted esters are intrinsically more reactive than the alkyl ester.[12] Using DMAP, the relative rates of methanolysis of the PNP esters of propionic acid, methoxyacetic acid, and glycolic acid are 30, 213, and 690 (Figure 1). However, using FPP under the same conditions, the relative rates of methanolysis of the PNP ester of propionic acid, methoxyacetic acid, and glycolic acid are 1, 5.3, and 511 (Figure 1). Thus, with FPP, methanolysis of the PNP ester of glycolic acid is 96 times faster than that of the PNP ester of methoxyacetic acid, whereas with DMAP it is only 3.2 times faster. This difference is primarily due to a 40-fold decrease in the rate of the methanolysis of the methoxy-substituted compound with FPP ($k_{rel} = 5.3$) as compared to DMAP ($k_{rel} = 213$), consistent with our proposed mechanism of action for FPP (*vide supra*).

FPP is also effective for the methanolysis of esters less active than PNP esters. Under the same conditions as in the previous study, the relative rates of methanolysis of phenyl glycolate, *p*-fluorophenyl glycolate, and *p*-nitrophenyl glycolate are 64, 140, and 510 with a half-life for the phenyl glycolate methanolysis of 18 h (Figure 2). These relative rates are comparable to those observed for simple alkaline hydrolysis.[13]

FPP was designed to function as a nucleophilic catalyst and to proceed via the cyclic acylpyridinium species **3** shown in Scheme 1. There is ample evidence that this type of species is accessed by PPY and DMAP as an intermediate in the catalytic cycle. However, our preliminary data suggest that this mechanism is *not* operating in this system, and that the pyridine acts as a base rather than a nucleophile. For example, we have examined the reaction of the PNP ester of glycolic acid and the pentafluorophenyl ester of glycolic acid with FPP in $CDCl_3$ in the absence of methanol and do not observe the acylpyridinium species. Instead, lactone acetal **2** is rapidly and cleanly formed (Scheme 1).[14] If an excess of the glycolate is present, acyl

Scheme 1



transfer to the glycolate occurs to provide the corresponding dimer, trimer, and higher oligomers, suggesting that the lactone acetal is a kinetically competent intermediate along the reaction pathway.[15]

In conclusion, we have described a new and selective catalyst for the methanolysis of α-hydroxyaryl esters which operates by a novel mechanism. We are currently engaged in efforts to determine the details of the mechanism and scope of this reaction, and the design of chiral variants of this catalyst.

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Supporting Information Available: Experimental details for the preparation of **1**, ^{1}H and ^{13}C NMR spectral data for **2**, and procedure for the determination of the methanolysis kinetics (6 pages). See any current masthead page for ordering and Internet access instructions.

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(12) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1953; pp 757−758.

(13) The relative rate of simple alkaline hydrolysis of PNP and phenyl esters is 3.5:1, a value which is comparable to what we observe with our catalyst. See: Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145.

(14) This intermediate has been characterized by ^{1}H and ^{13}C NMR spectroscopy. See the supporting information for details.

(15) This mechanism is related to that reported by Menger in which a micellar aldehyde hydrate serves as a nucleophilic catalyst for the hydrolysis active esters. See ref 1e.