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# TETRAFLUOROPYRROLIDINE

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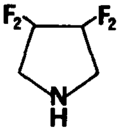
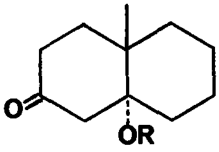
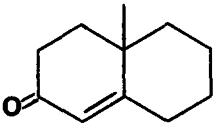
Weakly basic primary amines, such as cyanomethylamine (CMA, $pK_a$=5.34), are excellent catalysts via iminium ion formation for decarboxylation of acetoacetate[1] and α proton abstraction from carbonyl compounds.[2,3] We have been interested in studying even more weakly basic nucleophilic amine catalysts, and because pyrrolidine is exceptionally good at condensing with carbonyl groups,[4] our interest focused initially on the novel 3,3,4,4-tetrafluoropyrrolidine (TFP, 1). Synthesis of TFP was accomplished by reduction of 3,3,4,4-tetrafluorosuccinimide[5] with borane in THF.[6] TFP was isolated as TFP·HCl[7] (68% sublimed); NMR($DMSO-D_6$): $^1H$ δ 4.07 (m,4) and 9.25 ppm (s,2); $^{19}F$ δ 41.74 ppm upfield from TFA(m). The $pK_a$ of TFP determined by the half-neutralization method (25°, μ=0.4) is 4.05.



1



2, R = H
3, R = Ac



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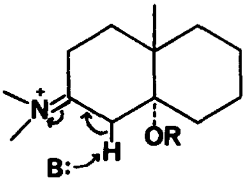


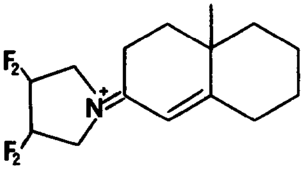
5, B = >NH
6, B = $H_2O$

TFP is the best monofunctional nucleophilic catalyst for α deprotonation yet reported. Its effectiveness was evaluated using decalones 2[8] and 3[9], which lead irreversibly to formation of enone 4 after rate limiting proton abstraction through transition states 5 and 6[10], in the same manner as delineated previously for the *cis*-fused isomers of 2 and 3.[2,3] The rate constants, $k_{AB}$ and $k_A$, characterizing formation of 4 from 2 or 3 via 5 and 6 respectively are larger than those found previously with any of six primary amines ranging in base strength from *n*-butylamine ($pK_a$=10.61) to CMA.[11]

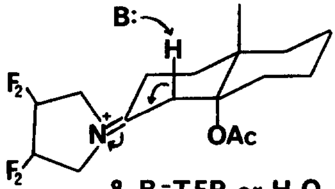
Catalysis by TFP differs from catalysis by CMA and other primary amines[2,3] because enimmonium ion 7 [$\varepsilon_{286}(H_2O)$ 2.9 x $10^4$; δ ($CH_3OD-D_2O$) 6.53 ppm] appears not only as an intermediate[12], but also in a readily detectable equilibrium amount even at relatively low catalyst concentrations. The approach to equilibrium between 4 and 7 was studied using preformed 4 by following either disappearance of 4 at 247 nm or appearance of 7 at 286 nm. The results are consistent with equation (1); formation of 7 depends on [TFP·HCl] and $k_3=3 \times 10^{-3}M^{-1}sec^{-1}$; hydrolysis of 7 is independent of catalyst buffer concentration or ratio[13] and $k_2=1.5 \times 10^{-3}sec^{-1}$; $K=[7][H_2O]/[4][TFP\cdot HCl]=110$, about ten times greater than the K's for the comparable equilibria between primary amines and their enimminium ions.[14]

$$2 + \text{TFP·HCl} \xrightarrow{k_1} 7 + H_2O \underset{k_3}{\overset{k_2}{\rightleftharpoons}} 4 + \text{TFP·HCl} \tag{1}$$

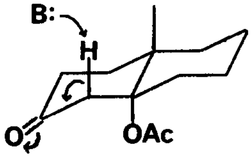
Conversion of 3 to 4 catalyzed by 1 M TFP solution at pH 4.05 has $t_{1/2} \cong 4$ min, and occurs more than 600 times via 8 for every time it occurs via 9[15]. It can be estimated that the rate constant characterizing 8 is at least $10^6$ greater than that for 9. It will be of interest to see if TFP is also an effective catalyst for decarboxylations, aldol condensations, etc.



**7**



**8, B=TFP or $H_2O$**



**9, B=TFP or $H_2O$**

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8. H.B. Henbest and J. McEntee, J. Chem. Soc., 4478 (1961).
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10. Large invariant primary kinetic isotope effects were observed (cf., refs. 2, 3) when appropriately deuterated 2 and 3 (ref. 9) were converted to 4 by TFP under conditions in which the $k_{AB}$ and $k_A$ terms dominated.
11. Pertinent rate constants: TFP, $k_{AB}^{2}=4.2 \times 10^{-3}M^{-2}sec^{-1}$, $k_{A}^{2}=2.5 \times 10^{-4}M^{-1}sec^{-1}$, $k_{AB}^{3}=9.8 \times 10^{-3}M^{-2}sec^{-1}$, $k_{A}^{3}=9.5 \times 10^{-4}M^{-1}sec^{-1}$; CMA, $k_{AB}^{2}=1.3 \times 10^{-3}M^{-2}sec^{-1}$, $k_{A}^{2}=1.5 \times 10^{-5}M^{-1}sec^{-1}$, $k_{AB}^{3}=4.1 \times 10^{-3}M^{-2}sec^{-1}$, $k_{A}^{3}=1.0 \times 10^{-4}M^{-1}sec^{-1}$.
12. H.E. Ferran, Jr., D.A. Drake, and T.A. Spencer, J. Org. Chem., 40, 2017 (1975).
13. These observations are consistent with the slow step in the hydrolysis being attack of water on 7, which might be expected to show general base catalysis (gbc). M. Brault, R.M. Pollack, and C.L. Bevins, J. Org. Chem., 41, 346 (1976) report $\beta=0.4$ and K. Koehler, W. Sandstrom, and E.H. Cordes, J. Am. Chem. Soc., 86, 2413 (1964) report $\beta=0.27$ for such processes. Our data on hydrolysis of 7, obtained only with TFP buffers, would probably have revealed gbc if $\beta \geq 0.3$.
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15. The rate constant, $k_B$, for direct α proton abstraction from 3 by TFP is $5 \times 10^{-6}M^{-1}sec^{-1}$.