Conversion of Aliphatic Amides into Amines with [*I*,*I*-Bis(trifluoroacetoxy)iodo]benzene. 2. Kinetics and Mechanism

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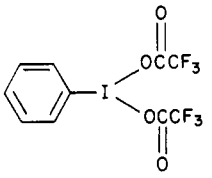
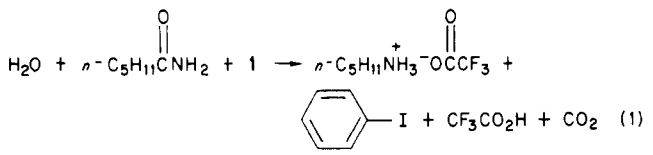
The reagent [*I*,*I*-bis(trifluoroacetoxy)iodo]benzene (PIFA), used to prepare amines from amides as described in the preceding paper, dissolves in 50:50 (v/v) aqueous acetonitrile to give an acidic solution. This behavior can be explained quantitatively by the dimerization of PIFA in solution under preparatively significant conditions; the dimer, μ-oxo-*I*,*I*'-bis(trifluoroacetato-*O*)-*I*,*I*'-diphenyldiiodine(III), **2**, can be isolated from the reaction mixture above pH 3. The rate of hexanamide rearrangement by PIFA was studied as a function of PIFA concentration and shown to display asymptotic behavior. The rate is depressed by added trifluoroacetate and accelerated by increasing pH, but not in a simple way. These observations can be accounted for by a mechanism (eq 13–15) in which the dimer **2** complexes with the amide, releasing acid. It is this released acid that accounts for most of the kinetically significant observations. The rearrangement of the amide–dimer complex is the rate-limiting step. Other kinetically indistinguishable mechanisms are also possible. The rate of rearrangement promoted by dimer alone is in agreement with that predicted by the proposed mechanism. The imidic acid (enol) form of the amide is considered as a possible kinetically active form of the amide but is rejected on kinetic grounds.

[*I*,*I*-Bis(trifluoroacetoxy)iodo]benzene (**1**), to which we refer by the acronym PIFA, has been shown to be an effective reagent for the oxidative conversion of aliphatic amides into amines.[1] In this paper, we consider the mechanistic aspects of this conversion. For the most part, our mechanistic studies utilized the oxidative conversion of hexanamide to 1-pentanamine, a reaction very typical of others promoted by PIFA that proceeds in excellent yield (eq 1).



1 (PIFA)



(1)

Results and Discussion

Characteristics of PIFA in Aqueous Solution. Much of the key to understanding how PIFA brings about the amide-to-amine conversion in aqueous solution hinges on an understanding of the nature of the reagent itself in aqueous solution. Although the reagent **1** has no acidic protons, it was interesting to find that it dissolves in aqueous acetonitrile to give a rather acidic solution. The acidity of aqueous PIFA solutions is not due to trifluoroacetic acid solvation of the crystalline material because the crystalline material gives an excellent elemental analysis. Furthermore, aqueous solutions of PIFA show a single line in the ^{19}F NMR (although this result does not rule out rapid exchange of trifluoroacetate between trifluoroacetic acid and PIFA). On the reasonable assumption that the acid released is trifluoroacetic acid, it was important to be able to measure the trifluoroacetic acid released in a simple manner. First, the pH meter was calibrated for 50:50 v/v aqueous acetonitrile (hereafter called the solvent) by measuring the pH of standard HCl solutions in this solvent system. There was found to be an excellent linear relationship between the pH meter reading, pH_{meter}, and the pH, taken to be $-\log [H^+]$:

$$pH = 1.13pH_{meter} - 0.056 \quad (2)$$

In all subsequent discussion, the term pH refers to meter readings corrected according to eq 2. The pH thus measured therefore refers to the reference state of dilute solution in 50:50 (v/v) aqueous acetonitrile.

The pH values of solutions of known amounts of trifluoroacetic acid in the solvent were determined and were fit quantitatively to the mass action law for trifluoroacetic acid dissociation with a pK_a for trifluoroacetic acid of 0.90 ± 0.01 (Figure 1). The reference line of unit slope shown in Figure 1 would be followed if trifluoroacetic acid were completely dissociated; this line is approached, as it should be, at high dilution. In this and subsequent work the ionic strength could not be held constant for reasons that will be elaborated below. This determination allowed us to relate the pH of a solution to the stoichiometric trifluoroacetic acid concentration; that is, the pH meter reading would thus serve as our "indicator" for trifluoroacetic acid provided that no other sources of protons are present.

The pH of solutions of PIFA at various concentrations in the solvent was examined next (Figure 2). This figure clearly shows that increasing PIFA concentrations increase the acidity of the solution. This proton release by PIFA could be quantitated by either of two schemes. In the first, PIFA, P, dissociates to some other species, M, and 1 equiv of trifluoroacetic acid, which then ionizes to provide the protons (eq 3 and 4). In this and subsequent schemes,

$$H_2O + P \overset{K_1}{\rightleftharpoons} M + HA \quad (3)$$

$$HA \overset{K_a}{\rightleftharpoons} H^+ + A^- \quad (4)$$

HA is undissociated trifluoroacetic acid and A^- is trifluoroacetate ion. Mass balance and the equilibrium constant expressions for eq 3 and 4 lead to the following

(1) Loudon, G. M.; Radhakrishna, A. S.; Boutin, R. H.; Blodgett, J. K.; Almond, M. R. *J. Org. Chem.*, preceding paper in this issue. The nomenclature of this compound is discussed in ref 4 of this paper.

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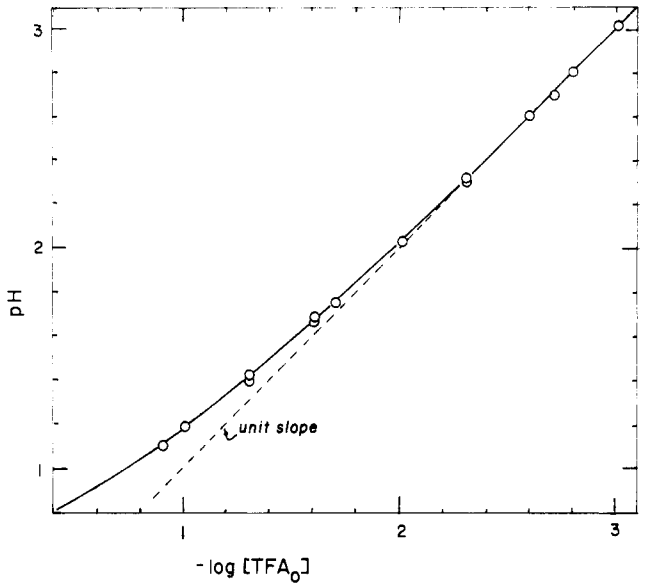


Figure 1. Determination of the pK_a of trifluoroacetic acid in 50:50 (v/v) acetonitrile–water. The pH was measured as a function of [TFA$_0$], the stoichiometric trifluoroacetic acid concentration. The points are experimental, and the solid line is calculated from the mass action law for dissociation using a pK_a of 0.90. The dashed reference line of unit slope is approached in the limit of complete dissociation at infinite dilution.

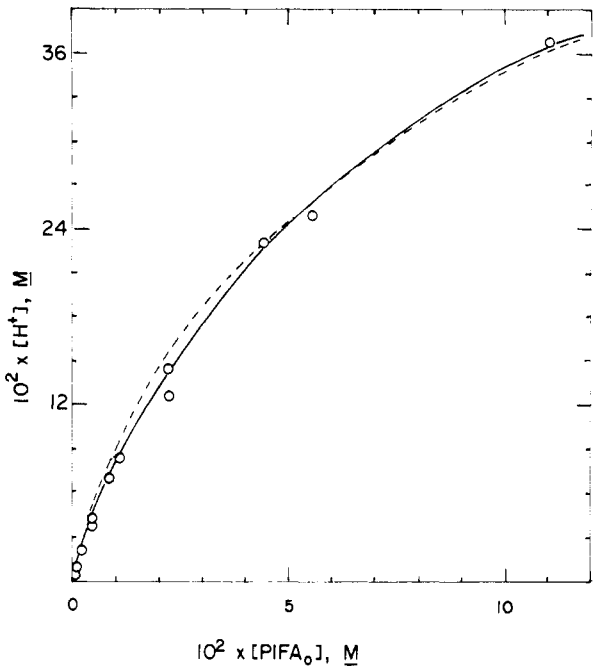


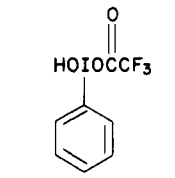
Figure 2. Release of acid as a function of the stoichiometric concentration of PIFA (1). The points are experimental, and the solid line is calculated from eq 9 with a K_D of 6.7×10^{-4} M. The dashed line is calculated from eq 5 with a K_1 of 7.7×10^{-3} M.

equation, which was used to fit the data. In this equation,

$$[P_0] = \frac{[HA_t][HA]}{K_1} + [HA_t] \quad (5)$$

$[P_0]$ is the stoichiometric PIFA concentration and $[HA_t]$ is the stoichiometric trifluoroacetic acid concentration, that is, [HA] + [A$^-$]. The K_a value for trifluoroacetic acid dissociation determined above was used to fit the data with a nonlinear least squares analysis;[2] this analysis gave for K_1 a value of $(7.7 \pm 0.3) \times 10^{-3}$ M, where the water concentration is incorporated into the value of K_1. This fit is shown as the dashed line in Figure 2.

One reasonable structure of M that fits the stoichiometry of eq 3 and has ample literature precedent is [*I*-hydroxy-*I*-(trifluoroacetoxy)iodo]benzene:



possible structure of M

The [*I*-hydroxy-*I*-[(*p*-tolylsulfonyl)oxy]iodo]benzene studied by Koser[4] is an example of such a compound.

When carrying out measurements of this type it is usually important to use a high concentration of an inert electrolyte in order to maintain constant ionic strength. Addition of KCl to solutions of PIFA gave immediately a precipitate of phenyl iodosyl dichloride, PhICl$_2$, a known free-radical chlorinating agent. Other weak-base anions, such as nitrate, sulfonate, etc., are also known to form *covalent* linkages with the iodine in trivalent PhIX$_2$ derivatives, even in aqueous solution,[3,4] and the nature of the anion appears to affect the chemistry observed. Even added trifluoromethanesulfonate (triflate) greatly depressed the rate of the reaction. We felt that release of even small amounts of HF or F$^-$ from anions such as BF_4^- or PF_6^- in the acidic solutions employed would also affect the chemistry observed and, furthermore, would be disastrous to the glass electrode used to follow the reaction. We were reluctant for safety reasons to use perchlorate as an "inert" electrolyte since PIFA is also an oxidizing agent. Thus we were left with no choice but to pursue our studies without maintaining constant ionic strength. However, as we shall show, a reasonably satisfactory mechanistic description can be advanced for the PIFA reaction under the assumption that ionic strength effects are minor.

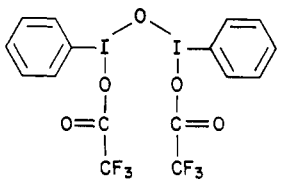
An important consequence of eq 3 and 4 taken together is that at high pH values mass action predicts that ionization of trifluoroacetic acid (eq 4) should pull the equilibrium of eq 3 to the right. Therefore, at sufficiently high pH, PIFA should be largely in the form of the material M. During our kinetic investigations we had occasion to raise the pH of a 0.25 M PIFA solution to about 4 with pyridine. Quite unexpectedly a light yellow precipitate appeared which was filtered and analyzed. The IR spectrum of this precipitate had absorptions at 1670 cm^{-1} (sh 1705 cm^{-1}) and 1130–1190 cm^{-1}. This was distinctly different from the IR spectrum of PIFA itself (1700, 1740 cm^{-1}) or iodosobenzene, PhI=O (no absorption 1600–1800^{-1}). The elemental analysis and cryoscopic molecular weight (660 ± 270; calcd 650) of this material are all consistent with the following structure, which is formally that of a PIFA

(2) Wentworth, W. E. *J. Chem. Educ.* **1965**, *42*, 96. The procedure discussed in this paper was written in Microsoft FORTRAN-80 and used with a North Star-Horizon microcomputer.

(3) Dasent, W. E.; Waddington, T. C. *J. Chem. Soc.* **1960**, 3350–3356.

(4) (a) Koser, G. F.; Wettach, R. H.; Troup, J. M.; Frenz, B. A. *J. Org. Chem.* **1976**, *41*, 3609–3611. (b) Koser, G. F.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1981**, *46*, 4324–4326.

dimer less a molecule of trifluoroacetic anhydride:



2(PIFA dimer)

μ-oxo-*I*,*I*'-bis(trifluoroaceto-*O*)-*I*,*I*'-diphenyldiiodine(III)

Alcock and Waddington[5] reported that evaporation of ether from an ether solution of PIFA gave a yellow gum, IR 1660, sh 1705 cm^{-1}, that changed rapidly into iodosobenzene and PIFA. The yellow gum was assigned the structure **2**. Evidently our isolation of **2** is the first isolation of this material in reasonably pure form. Unfortunately it proved impossible in our hands to crystallize **2** in a form suitable for X-ray diffraction analysis, although structures analogous to **2** have been postulated for other compounds.[5,6] The precipitation of this dimer prevented study of the rearrangement reaction at pH values much higher than 3.3.

A solution of 0.125 M **2** and 0.25 M TFA oxidizes hexanamide with essentially the same rate (apparent second-order rate constant 0.651 M^{-1} min^{-1}) as a 0.25 M solution of PIFA itself (0.641 M^{-1} min^{-1}) under otherwise identical conditions. This experiment shows that a solution of PIFA and a solution of dimer **2** are *kinetically equivalent*, although it of course does not prove that the dimer is the kinetically active species in solutions of PIFA.

The isolation of dimer **2** led us to consider a second scheme to account for acid release by PIFA. With the formation of **2** as the source of trifluoroacetic acid, the data of Figure 2 were treated to the scheme in eq 6 and 7. In

$$H_2O + 2P \overset{K_D}{\rightleftharpoons} D + 2HA \quad (6)$$

$$HA \overset{K_a}{\rightleftharpoons} H^+ + A^- \quad (7)$$

this scheme, P = PIFA and D = dimer **2**, and the K_D is defined to include the water concentration:

$$K_D = \frac{[D][HA]^2}{[P]^2} \quad (8)$$

Mass balance considerations, along with eq 8, lead to eq 9 in terms of measurable quantities. In this equation, $[P_0]$

$$[P_0] = \left(\frac{[HA_t][HA]^2}{2K_D}\right)^{1/2} + [HA_t] \quad (9)$$

is the stoichiometric concentration of PIFA. This equation was fit to the data shown in Figure 2 by using the pK_a of trifluoroacetic acid determined above, 0.90, and treating K_D as a disposable parameter. This gave a K_D of $(6.7 \pm 0.3) \times 10^{-4}$ M; the solid line in Figure 2 is calculated from this value. Despite the different functional forms of eq 5 and 9, the data in Figure 2 do not distinguish between a monomeric M form of PIFA (dashed line, eq 3) and the dimer (solid line, eq 6) as the major species *in solution*. Furthermore, subsequent kinetic experiments could be interpreted equally well in terms of either dimer D or monomer M. Because the dimer D was actually isolated from the reaction mixture, we have arbitrarily chosen to interpret the kinetic data in terms of D as the kinetically active species. These experiments, like any kinetic experiments, of course cannot differentiate among other models that fit the data equally well.

Kinetic Studies of the Rearrangement Reaction. Because trifluoroacetic acid is liberated in the rearrangement of amides by PIFA (eq 1), we believed that it would be simplest to follow the rearrangement of hexanamide titrimetrically on a pH-stat. In our initial studies, carried out prior to the work described in the previous section, we followed the rate of the reaction over its entire course, but we found that the release of protons is complex and does not follow a simple kinetic order. It is now clear why this behavior is observed. First, when PIFA is dissolved in the solvent protons are liberated because of dimer formation, as shown in eq 6 and 7. The pH of the reaction mixture is adjusted at this point before amide is added, so these protons do not contribute to the observed proton release during amide rearrangement. The rearrangement of amide to isocyanate results in the release of 1 equiv of trifluoroacetic acid per mole of amide (eq 10). However, the

$$2RC(O)NH_2 + D \rightarrow 2PhI + 2RN{=}C{=}O + 2CF_3CO_2H + H_2O \quad (10)$$

subsequent hydrolysis of the isocyanate under the reaction conditions produces a basic amine, which, under the reaction conditions, is protonated—that is, takes up 1 equiv of protons (eq 11). Thus, if hydrolysis of the isocyanate

$$RN{=}C{=}O + CF_3CO_2H + H_2O \rightarrow RNH_3^+ + CO_2 + CF_3CO_2^- \quad (11)$$

is contributing to the proton inventory, protons would be liberated until the isocyanate concentration reaches a maximum value and then protons would be consumed. This behavior was indeed observed experimentally. Therefore, if the rearrangement reaction is to be followed by titrimetry, it is necessary to work under conditions such that the isocyanate hydrolysis is slow. The intermediate in the reaction, *n*-pentyl isocyanate, was synthesized and its reaction rate determined at various pH values in our solvent and compared to the overall rate of proton release during amide rearrangement. As expected,[7] over the pH range 1–3, the hydrolysis rate was slowest at the higher pH values. At pH 2.99, for example, the hydrolysis of the isocyanate is sufficiently slow that it would reduce the proton release by *at most* 4%. At lower pH values, however, isocyanate hydrolysis has a progressively greater effect on proton release. A further complication of the reaction at all pH values is that the byproduct iodobenzene comes out of solution as the reaction proceeds. To the extent that iodobenzene extracts the reacting amide and/or PIFA from solution, the kinetics will deviate from ideal behavior. To minimize both the effect of isocyanate hydrolysis and iodobenzene accumulation on the observed proton release, we used an initial rate technique to study the kinetics. That is, the rates were calculated from the first few percent reaction. In these early stages of the reaction, the amount of isocyanate produced is minimal and its hydrolysis can be ignored, and the amount of iodobenzene in the kinetic solution is minimized.

In measuring rates using proton release, it is important to be able to correlate the moles of protons released with the moles of amide reacted, i.e., with the actual progress of the reaction. Because PIFA forms dimer **2** in solution,

(5) Alcock, N. W.; Waddington, T. C. *J. Chem. Soc.* **1963**, 4103–4109.
(6) Neiland, O. Ya.; Karele, B. Ya. *J. Org. Chem. (USSR)* **1970**, 885–886.
(7) Williams, A.; Jencks, W. P. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 1753.

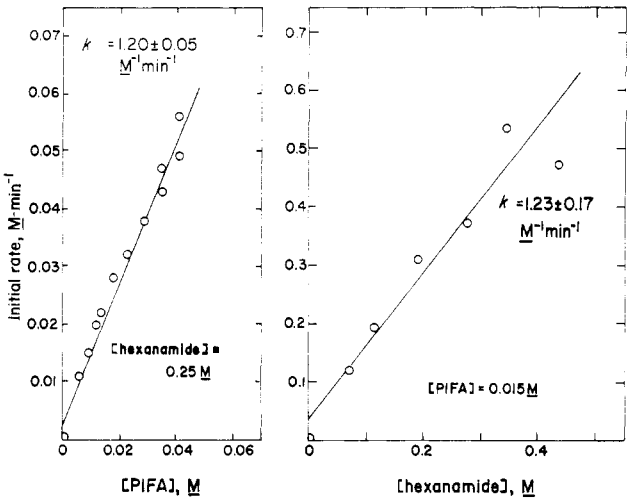


Figure 3. Initial rates as a function of PIFA and hexanamide concentrations at low [PIFA], pH = 2.99. For the experiments in the left panel, [hexanamide] was held constant and [PIFA] varied. For the right panel, [PIFA] was held constant and [hexanamide] varied.

the number of protons released depends on the amount of dimer in solution, and this varies with pH (eq 6 or 7). For example, if there is no dimer in solution, rearrangement to the isocyanate releases two protons (eq 12). (At

$$H_2O + RC(O)NH_2 + PhI(OC(O)CF_3)_2 \rightarrow RN{=}C{=}O + PhI + 2CF_3CO_2H \quad (12)$$

the pH values used, trifluoroacetic acid is completely ionized, so trifluoroacetic acid concentration can be equated with proton concentration.) On the other hand, if PIFA is entirely in the dimer form, the rearrangement only releases one proton (eq 10); the additional proton is released by dimer formation, which occurs before amide is added. Titration of 0.25 M PIFA with 0.25 M pyridine revealed that 1 equiv of titrant is required to bring the PIFA solution to a pH of 2.99. Thus, at pH 2.99, all PIFA is in the dimer form. The proton balance for the overall reaction then requires that at this pH the rearrangement will release one additional proton. However, at successively lower pH values, PIFA in solution contains less of the dimer form and therefore more protons are released during the rearrangement. Using similar pyridine titrations, we could relate the proton release to the reaction progress at different pH values.

The initial rate of the rearrangement reaction at pH 2.99 was determined at constant [hexanamide] and varying [PIFA] in a series of experiments. The converse series of experiments, measuring the initial rate at constant [PIFA] and varying [hexanamide], was also carried out. The results of both sets of experiments, shown in Figure 3, gave the same second-order rate constant: 1.2 ± 0.1 M min^{-1}. An interesting and revealing result was obtained, however, when the range of PIFA concentrations was extended beyond that shown in the left panel of Figure 3. At PIFA concentrations higher than about 0.1 M, the rate (within the precision of the data) appears to level off and approach an asymptotic limit, as shown in Figure 4. This concentration range is important because it is the range that is used under typical preparative conditions.

Another interesting experiment involved the variation of the rearrangement rate with pH. It was found that even though the rearrangement occurs under moderately acidic conditions, *its rate increases with increasing pH*. This is undoubtedly the source of the "pyridine catalysis" observed in PIFA-promoted amide rearrangements (see

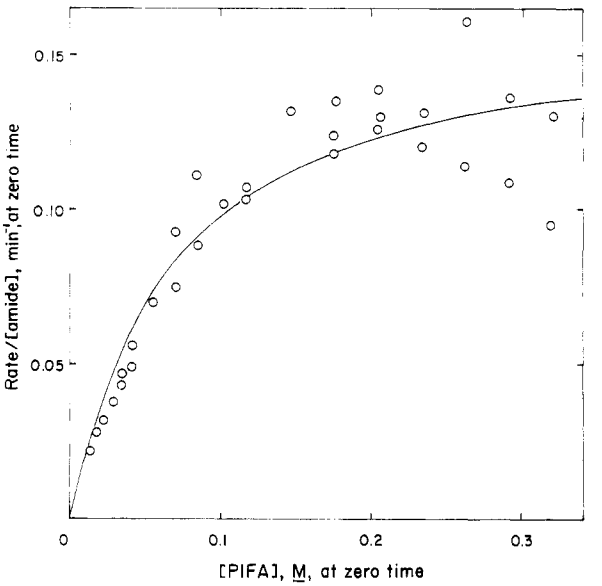


Figure 4. Initial rates as a function of [PIFA] at a constant hexanamide concentration of 0.25 M and pH of 2.99. The data used in this figure are given in Table II in the supplementary data.[17] The points are experimental, and the curve is calculated from the parameters in Table I.

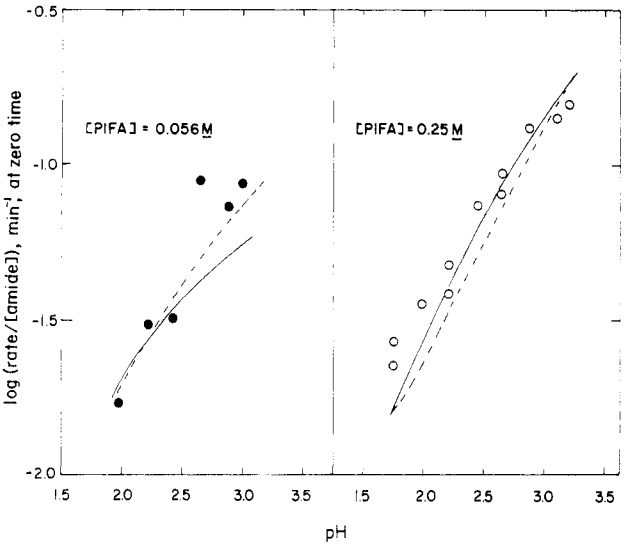


Figure 5. Initial rates as a function of pH at two different PIFA concentrations. The data used in this figure are given in Table III in the supplementary data.[17] The points are experimental, and the solid curve is calculated from the "best-fit" parameters in Table I. The dashed curve is calculated from the parameters used for the curve in Figure 4.

Figure 1, previous paper[1]). Yet the log rate vs. pH profile, shown in Figure 5, does not appear to approach any integral slope.

A third type of experiment bearing on the mechanism of the reaction involved measuring the rates of the rearrangement at constant pH but with increasing amounts of exogenously added trifluoroacetate ion. In these experiments extra trifluoroacetic acid was added prior to addition of amide and the pH was adjusted with pyridine. As shown in Figure 6, the rate at constant pH decreases with increasing trifluoroacetate.

Mechanism of PIFA-Promoted Hexanamide Rearrangement. Ideally, a mechanism for the PIFA-promoted rearrangement should predict the kinetic behavior shown in Figures 4–6—that is, the asymptotic behavior with increasing [PIFA], the rather unconventional pH–rate pro-

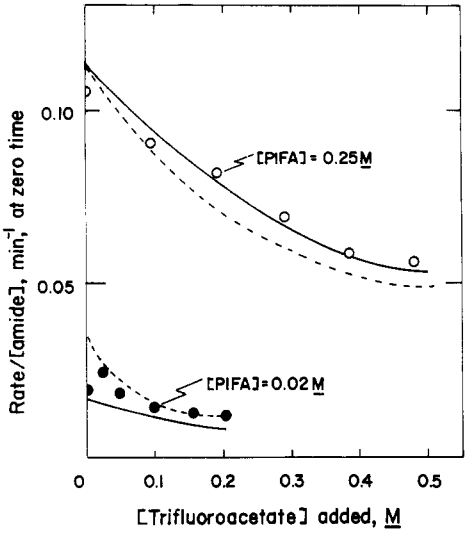


Figure 6. Initial rates as a function of exogenously added trifluoroacetate at pH 2.99 and two different PIFA concentrations. The data used in this figure are given in Table IV in the supplementary data.[17] The points are experimental, and the solid line is calculated from the "best-fit" parameters in Table I. The dashed curve is calculated from the parameters used for the curve in Figure 4.

file, and the decrease in rate with added trifluoroacetate. A mechanism that predicts all of these phenomena is shown in eq 13–15. In this mechanism X is a complex

$$\underset{\text{amide}}{D + RC(O)NH_2} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [X] + HA \tag{13}$$

$$HA \overset{K_a}{\rightleftharpoons} H^+ + A^- \tag{14}$$

$$[X] \xrightarrow{k_3} \text{products} \tag{15}$$

between dimer and amide and, as above, HA is trifluoroacetic acid. Assuming that X is in steady state, the following rate law is predicted by this mechanism:

$$\frac{\text{initial rate}}{[\text{amide}]} = \frac{fk_1[D]}{1 + (k_2/k_3)[HA]} \tag{16a}$$

In this equation, initial rate refers to the observed rate of proton release, the concentrations are those at zero time, and f is a factor that corrects for number of protons released per equivalent of reaction:

$$f = \frac{2}{[P_0]}([D] + [P]) \tag{16b}$$

That is, when the dimer D is the major species present in solution, the rate of product formation is equal to the rate of proton release; when PIFA (P) is the major species in solution, the rate of proton release is equal to twice the rate of reaction. The factor f is of course a function of pH, $[P_0]$, the trifluoroacetic acid concentration, as one can see from eq 6 and 7, but actually represents a relatively small correction to the data under most experimental conditions studied. In all kinetic experiments the concentrations of P and D under a given set of conditions were calculated from mass balance and eq 8 or appropriate derived relationships under the conditions prevailing at each experimental point.

Before considering the more detailed mathematical analysis of the data, it is appropriate to show in a general conceptual way why this mechanism and rate law are appropriate to describe the rearrangement of hexanamide by PIFA. At first sight it is puzzling that this rate law can account for the asymptotic behavior in Figure 4, since there is no term for PIFA (or dimer) in the denominator. However, we have already shown that the dimerization of PIFA releases acid (eq 6). According to this equation, the following mass balance then exists:

$$[HA_t] = [HA] + [A^-] = 2D \tag{17}$$

This follows since any trifluoroacetic acid (HA) or trifluoroacetate (A^-) free in solution must originate from PIFA. The [HA] concentration can therefore be rewritten in terms of dimer concentration (eq 18). In this equation,

$$[HA] = 2D\left(\frac{[H^+]}{K_a + [H^+]}\right) \tag{18}$$

the expression in parentheses is the fraction of trifluoroacetic acid in the unionized form. Substituting this expression into eq 16a, we have eq 19. This expression has

$$\frac{\text{initial rate}}{[\text{amide}]} = \frac{fk_1[D]}{1 + (k_2/k_3)(2[D])\left(\frac{[H^+]}{[H^+] + K_a}\right)} \tag{19}$$

dimer D in the denominator. Since the dimer concentration increases with increasing PIFA concentration, eq 19 predicts qualitatively the asymptotic behavior observed in Figure 4. In other words, *the addition of PIFA to the solution causes an increase in the dimer formation and, because of eq 6 and 7, an increase in the trifluoroacetic acid concentration.* It is not the additional PIFA itself that is causing the rate to level off but rather the trifluoroacetic acid liberated from the PIFA.

It is also clear that a kinetic scheme like eq 13–15 can equally apply if monomer M of eq 3 replaces D in eq 13. In such a case M replaces D in the numerator of eq 19, M replaces 2 [D] in the denominator, M/2 replaces D in f (eq 16b), and a functionally equivalent rate expression results.

The mechanism in eq 13–15 also predicts qualitatively an increase in the rate with pH. The term $([H^+]/(K_a + [H^+]))$, the fraction of unionized trifluoroacetic acid, in the denominator of eq 19 arises from the fact that *unionized* trifluoroacetic acid is liberated in the first step of the mechanism (eq 13). Lowering the pH will *increase* the fraction of unionized trifluoroacetic acid, thus pushing the equilibrium of eq 13 back toward starting materials and decreasing the steady-state concentration of X. Raising the pH removes trifluoroacetic acid from solution (as the trifluoracetate ion: eq 14) and tends to increase the steady-state concentration of the intermediate X. But there is a second pH effect superimposed on this one, as shown in eq 6 and 7. The amount of dimer, and thus the reactive form of PIFA, is also increased by increasing pH by the same mass law effect. Thus the pH effect on eq 19 is complex but clearly will cause a qualitative increase in rate with increasing pH.

Finally the mechanism above also predicts the effect of added trifluoroacetate anion at constant pH shown in Figure 6. Added trifluoroacetate pushes the equilibrium of eq 14 back toward unionized trifluoroacetic acid; and the increased trifluoroacetic acid concentration suppresses the rate by its mass action effect on the concentration of X in eq 13. In addition, added trifluoroacetate decreases the fraction of PIFA that exists as dimer by a similar mass action effect in accord with eq 6 and 7. Thus, increasing trifluoroacetate concentration should suppress the rate, as it does. Of course, superimposed on this effect is any effect of changing ionic strength, which, as we noted above,

could not be assessed in this work.

The kinetic data were treated quantitatively by using the mechanism in eq 13–15. First the initial rate data in Figure 4 was fit to eq 19 by using the kinetic constants k_1 and k_2/k_3 as disposable parameters. The amount of dimer present at any nominal PIFA concentration and pH could be calculated from the data in Figure 2 by using eq 20,

$$[P_0] = \left(\frac{[D]}{K_D}\right)^{1/2}(2[D] + [A^-_{added}])\left(\frac{[H^+]}{K_a + [H^+]}\right) + 2[D] \quad (20)$$

derived by straightforward mass balance and equilibrium considerations from eq 9. In this equation $[P_0]$ is the stoichiometric PIFA concentration and $[A^-_{added}]$ is the amount of exogenously added trifluoroacetate ion (zero in the experiments of Figure 4). This equation cannot by analytically solved for [D], but for any value of $[P_0]$ the value of [D] was calculated by successive approximations. In making this calculation, we could use the value of K_D determined from the data in Figure 2. However, the kinetic data of Figure 4 were determined at pH 2.99, whereas the data in Figure 2 were gathered at much lower pH values. (It was experimentally impossible to overlap the two sets of experiments, since initial rate data could not be obtained at lower pH for the reasons given above, and since pH 3 was not a realizable pH for any significant PIFA concentration in Figure 2.) However, there is an independent check on K_D that was also used. From eq 20 we found that the K_D value derived from the data in Figure 2 predicts that an 0.25 M solution of PIFA should be about 80% dimerized at pH 3. Since one proton is released for each PIFA dimerized, titration of an 0.25 M solution of PIFA to pH 3 should then require about 0.8 equiv of base. In fact we found that titration of PIFA to pH 3 requires 1.0 equiv of base; that is, there is evidently more trifluoroacetic acid in solution than predicted by the K_D determined from Figure 2. There are several reasons why this could be the case. For example, there seems to be no question that PIFA can lose 2 equiv of trifluoroacetic acid at sufficiently high pH to produce iodosobenzene (eq 21).

$$PhI(OC(O)CF_3)_2 \rightarrow PhI{=}O + 2CF_3CO_2H + H_2O \quad (21)$$

We know this is true because we found that a solution of 0.25 M iodosobenzene in 2 equiv of trifluoroacetic acid behaves kinetically exactly like a 0.25 M solution of PIFA. By microscopic reversibility, if PIFA (or dimer) can form from iodosobenzene, the reverse reaction may also occur. This second ionization may be significant near pH 3, but the titration data could not be fit to such a scheme in any simple way. Another reason for the discrepancy may be that ionic strength or medium effects have been ignored out of necessity, and these may be important. It is *not* likely, however, that the pyridine titrant causes any specific effects because titration with NaOH gives the same rates. Whatever the reason, we fit the data of Figure 4 with eq 19 twice, using successively the K_D value obtained from Figure 2 (6.7×10^{-4} M) and the K_D required to give a pH of 2.99 with 1 equiv of pyridine (1.87×10^{-2} M). The value of K_a for trifluoroacetic acid obtained earlier was used for this and subsequent calculations. About the same quality of fit was found in either case; only the kinetic constants obtained differ somewhat. This is undoubtedly because even for a 25-fold ratio of K_D the amounts of dimer predicted for the two K_D values differ by only 20% at pH 3. The kinetic constants for the fit using the larger K_D are given in Table I.

The pH dependence of the rate constant $[P_0]$ provides another way of estimating the kinetic parameters. Two series of experiments were done, each at a different values of $[P_0]$. At each pH an apparent K_D was calculated from the amount of pyridine required to titrate the starting PIFA solution to the indicated pH. The solid line in Figure 5 is the best fit of the rate expression to all the data and is calculated with the kinetic constants given in Table I. The dashed line is calculated by using the kinetic constants derived from the fit to the data in Figure 4.

Table I. Kinetic Constants for the Mechanism of Equations 13–15 Derived from Different Experiments

source: data in	k_1,[a] M^{-1} min^{-1}	k_2/k_3,[a] M^{-1}
Figure 4	4.7 ± 0.6	1800 ± 700
Figure 5	2.5 ± 0.5	630 ± 230
Figure 6	2.1 ± 0.2	520 ± 90

[a] Errors are standard deviations.

Finally, the rate data as a function of added trifluoroacetate anion at pH 2.99 (Figure 6) and constant $[P_0]$ (again at two different $[P_0]$ values) were fit by using eq 22,

$$\frac{\text{initial rate}}{[\text{amide}]} = \frac{fk_1[D]}{1 + 2(k_2/k_3)(2[D] + [A^-_{added}])\dfrac{[H^+]}{K_a + [H^+]}} \quad (22)$$

which is derived much like eq 19, and a K_D of 1.87×10^{-2} M. The solid line in Figure 6 is the best fit to all data and is calculated from the kinetic constants also given in Table I. The dashed line is calculated from the constants obtained in fitting Figure 4.

The data of Figures 4–6 all provide different ways of estimating k_1 and k_2/k_3. The agreement between the constants derived from Figures 5 and 6 is good, and the numbers obtained from Figure 4 are in order-of-magnitude agreement. Considering the limitations under which this work was carried out (inability to maintain constant ionic strength) and the wide variety of conditions employed, we cannot place great significance on the precise values of these numbers. What is important about them is that they all fit the proposed model at least semiquantitatively, and they all indicate that the rate-limiting step, eq 15, follows the acid-releasing complexation event (eq 13).

If the dimer **2** is in fact the "active species" it should be kinetically competent to bring about the rearrangement of amides. Since we had isolated the dimer, it was pertinent to test this point. Indeed, we found that 0.125 M dimer effected the rearrangement of hexanamide with an apparent second-order rate constant of 2.0 M^{-1} min^{-1}. Since this dimer solution was found to have an observed pH of 3.2, it is clear that it is disproportionating to at least a small extent. However, the amount of acid released is small, and the second term in the denominator of eq 19 can be ignored (it is estimated to be no more than 10^{-3}). Under these conditions, the second-order rate constant should equal k_1; from Table I, we see that this equality is realized at least for the last two entries.

Although our model apparently provides a reasonable fit to the data, we add again the cautionary note that there are kinetically indistinguishable mechanisms that would fit the data equally well. We have already noted the virtual equivalence of D and monomer M of eq 3 as the assumed kinetically active species. Another kinetically indistinguishable mechanism that predicts a rate law of the same functional form involves the formation of the dimer **2** (D in the equation below) as a *nonproductive* intermediate, and PIFA (P) as the kinetically active species (eq 23–25).

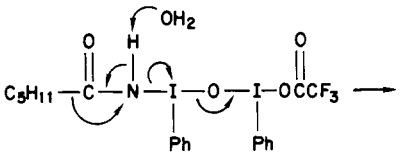
$$2P \overset{K_D}{\rightleftharpoons} D + 2CF_3CO_2H \quad (23)$$

$$\text{amide} + P \underset{k_2'}{\overset{k_1'}{\rightleftharpoons}} X' + CF_3CO_2H \quad (24)$$

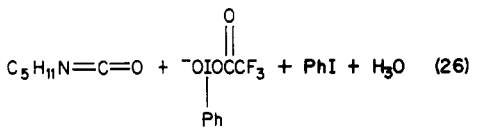
$$X' \xrightarrow{k_3'} \text{products} \quad (25)$$

In this mechanism, X′ is the complex between PIFA and amide. We currently have no reason to rule out this mechanism.

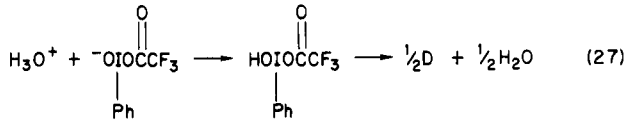
Complexation between Dimer and Amide. Our kinetic studies, of course, do not provide detailed structural evidence about the nature of the complex X between trivalent iodine-containing species and amide (eq 13), but speculation is appropriate. We might reasonably formulate this complex **3** and the rearrangement as follows:



3

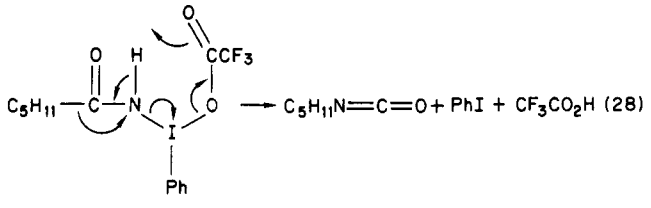


(26)



(27)

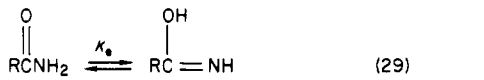
In the kinetically indistinguishable mechanism of eq 23–25, the analogous complex X′ might be formulated as **4** (eq 28).



(28)

4

In is also interesting to consider the mechanism of formation of such a complex. Since PIFA (or some species derived from it) is known to attack double bonds,[8] it seemed to us that one possible mechanism of complex formation would be for PIFA (or the dimer **2**) to attack the imidic acid, or enol, form of the amide **5** (eq 29 and 30). In an *experimental* test of this idea we allowed PIFA



(29)

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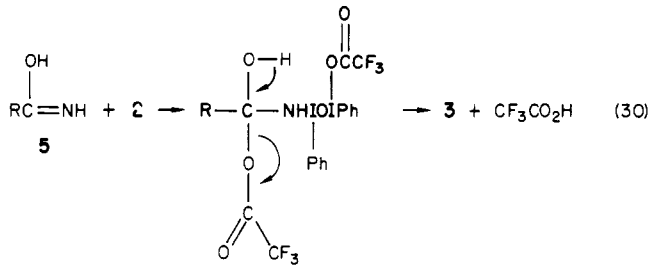

(30)

to react with methyl hexanimidate **6**—the methyl ester of the imidic acid—under the conditions of the rearrangement. After 5 h the solution was extracted with ether and the ether was treated with diazomethane. We isolated (by GC) a 72% yield of iodobenzene and a quantitative yield of methyl hexanoate. Under the reaction conditions **6** hydrolyzes more slowly than it reacts with PIFA.[9] Furthermore, PIFA was shown not to react with NH_3 under the reaction conditions. The fate of the imidate nitrogen could not be determined. Addition of methyl cinnamate to the reaction mixture gave no evidence of methyl 3-phenylpropionate, whch would have been formed[10] if the nitrogen were oxidized to diimide. Thus, PIFA is reduced by imidate esters, but the latter compounds are evidently not converted into isocyanates or amines in this reaction.

Theoretical considerations, however, suggest that PIFA (or its dimer) does *not* react with the imidic acid form of the amide. The value of K_e (eq 29) is known[11] to be about 10^{-8}, and the pK_as of protonated imidic acids ought to be similar to those of the analogous imidic esters:[9] about 7.5. The equilibrium concentration of unprotonated imidic acid at pH 3 is therefore about one part in $10^{12.5}$. From our kinetics, the second-order rate constant for reaction of dimer with amide is about 2 M^{-1} min^{-1} (Table I), or about 3.3×10^{-2} M^{-1} s^{-1}. In order to account for this observed rate, then, the second-order rate constant for reaction of dimer with the unprotonated imidic acid would have to be (0.033 M^{-1} $s^{-1}/10^{-12.5}$) or about 10^{11} M^{-1} s^{-1}, or faster than the diffusion-controlled limit. If the validity of our kinetic model is accepted, it therefore seems unlikely that the imidic acid form of the amide is the kinetically active species.

Rearrangement of the Complex. The kinetic data discussed above show that the rearrangement of the complex between amide and PIFA is rate-limiting. The relative rate data for various migrating groups (Table II, previous paper[1]) is qualitatively similar to that observed in similar reactions, such as the Lossen rearrangement, Hofmann rearrangement, and Baeyer–Villiger reaction. However, the relative rates cannot be considered exact measures of relative migratory aptitudes because of the pre-rate-determining equilibria involved in the reaction. The retention of stereochemistry observed in this reaction[1] is also analogous to that observed in other migrations to electron-deficient heteroatoms and shows that the migrating group is not released into solution as a free racemizable fragment such as a carbocation, carbanion, or radical.

Experimental Section

Melting points are uncorrected. Microanalysis was performed by the Microanalytical Laboratory of the Purdue Chemistry Department. All NMR spectra were obtained in chloroform-*d* on a Varian EM-360 NMR spectrometer at 60 MHz, and chemical shifts are reported as ppm downfield from Me_4Si. IR spectra were determined on a Beckman 33 spectrophotometer either between salts (neat liquids) or as a Nujol mull between polyethylene films (solids) made from commercial plastic wrap. This procedure was necessary because PIFA derivatives react with the halide ion in KBr. IR spectra are calibrated to polystyrene. Gas chromatography (GC) experiments were performed on a Hewlett-Packard Model 700 gas chromatograph using thermal conductivity detection. A $^1/_8$ in. × 6 ft. 10% SE-30 on Chromasorb W column, He flow rate 25 mL/m programmed from 70–180 °C at 5 deg/m, was used in all GC work.

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Hexanamide was prepared from hexanoic acid (Aldrich) by reaction with thionyl chloride and pouring of the reaction mixture into concentrated aqueous ammonia. The aqueous solution was extracted with methylene chloride, and the methylene chloride layer was dried over $MgSO_4$. Removal of the solvent in vacuo gave hexanamide (64% yield), mp 100–101 °C (lit.[12] mp 101 °C).

***n*-Pentyl isocyanate** was prepared from hexanoyl chloride (from hexanoic acid and thionyl chloride as above) and sodium azide by following an established procedure with some minor modifications.[13] The acetone solution containing the acyl azide was added to 50 mL of benzene and dried over $MgSO_4$ at 3 °C overnight. This was filtered and heated to 80 °C for 1 h. Removal of solvent by simple distillation and then vacuum distillation afforded *n*-pentyl isocyanate in 62% yield as a clear liquid; bp 39–40 °C (13 mm); IR 2900, 2270 cm^{-1}.

Methyl Hexanimidate (6). Equal amounts (51.5 mmol) of hexanenitrile and methanol (freshly distilled from 4-Å molecular sieves) were placed in a flask with 10 mL of absolute ether. The solution was saturated with dry HCl gas at 0 °C and allowed to stand overnight. Removal of solvent and unreacted starting materials on the rotary evaporator afforded a white solid (58% yield); mp 100–101 °C dec; lit.[14] mp 100–102 °C dec. The methyl acetimidate·HCl so obtained was converted into its free base by suspending the solid in ether and swirling for 5 min with 50 mL of 2 N $KHCO_3$. The ether layer was dried overnight over $MgSO_4$, filtered, concentrated on the rotary evaporator to a clear liquid, and distilled to afford methyl hexanimidate: bp 47–49 °C (10 mm); IR 3250, 3300, 2900, 1640 cm^{-1}; NMR δ 7.02 (1 H, br s), 3.75 (3 H, s), 2.25 (2 H, t, J = 7.5 Hz), 1.35 (6 H, m), 0.90 (3 H, t, J = 6 Hz).

[*I*,*I*-Bis(trifluoroacetoxy)iodo]benzene (PIFA, 1) was prepared as described previously.[1]

μ-Oxo-*I*,*I*'-bis(trifluoroacetato-*O*)-*I*,*I*'-diphenyldiiodine-(III) (Dimer 2). PIFA (1, 600 mg) was dissolved in 2.0 mL of acetonitrile, and then 2.0 mL of water was added and the pH was adjusted to 3.0 with pyridine. After some delay a pale yellow precipitate formed. This was filtered through a 10–15-μm glass frit, washed twice with water, and dried over P_2O_5 overnight in an Ar atmosphere. This material disproportionates under aspirator vacuum or on heating.[5] **Caution**: a small sample detonated at 220 °C during the melting point determination. Anal. (C, H, F, I) Calcd 29.56, 1.55, 17.54, 39.05. Found: 29.89, 1.74, 17.31, 38.71. IR: 1670, (sh 1705), 1130, 1190 cm^{-1}.

We attempted to determine the molecular weight of **2** by using a cryoscopic procedure in dioxane; as a control, the molecular weight of PIFA was also determined. The apparatus followed Shoemaker and Garland,[15] and the procedure followed Weissberger.[16] The low solubility of dimer **2** hampered this procedure, but the average of three determinations gave 660 ± 270 for this molecular weight (theoretical = 650); the molecular weight of PIFA was found to be 480 ± 80 (theoretical = 430) by the same procedure (four determinations).

Kinetic Procedures. Deionized distilled water was used in all experiments. Acetonitrile was HPLC grade, used as is. PIFA was placed in a jacketed titration vessel thermostatted at 25 °C and dissolved in 2.0 mL of acetonitrile. Water (2.0 mL) was then added. (PIFA dissolves very slowly in aqueous acetonitrile.) The pH was adjusted to the desired value by addition of pyridine. The reaction was begun by addition of amide as a solid; the amide dissolves rapidly. The release of protons was followed by automatic titration of the solution with a Radiometer Model TTTY-1C autotitrator equipped with recorder and combination electrode. The pH of the solutions was calibrated as described in the text by using standard HCl solutions in 50:50 (v/v) acetonitrile:water. For a typical initial rate determination the release of protons was followed for about the first 5–10% reaction by titration with a standard solution of pyridine in 50:50 (v/v) acetonitrile–water and the rate was calculated by taking the slope of the curve at zero time. The adjustment of pH and titration with standard NaOH solutions gave the same rate, but in some cases addition of NaOH during pH adjustment gave a precipitate that slowly dissolved. Pyridine, which did not give this precipitate, proved more convenient as a titrant for this reason.

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Registry No. 1, 2712-78-9; 2, 91879-79-7; hexanamide, 628-02-4; hexanoic acid, 142-62-1; hexanoyl chloride, 142-61-0; sodium azide, 26628-22-8; *n*-pentyl isocyanate, 3954-13-0; methyl hexanimidate, 57246-72-7; hexanenitrile, 628-73-9; methanol, 67-56-1; hexanoyl azide, 17228-07-8; methyl acetimidate·HCl, 14777-27-6.

Supplementary Material Available: Kinetic data used in constructing Figures 4–6 (3 pages). Ordering information is given on any current masthead page.

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(17) See paragraph at the end of this article regarding supplementary material.