228. The Acid-catalyzed Hydrolysis of CF_3-deactivated Diazoalkanes

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Summary

The acid-catalyzed hydrolysis of CF_3CHN_2 (**1**) follows an *A*2 mechanism of preequilibrium protonation and rate-determining solvolysis of the intermediate diazonium ion **4**; this was demonstrated by: a) the inverse kinetic isotope effect; b) H-D exchange; c) the unimportance of general acid catalysis; d) strong rate acceleration by added nucleophiles. The activation parameters have been determined in two solvent systems. In contrast to **1** the secondary diazocompound $CF_3-CN_2-CH_3$ (**2**) follows the normal A-S_E2 mechanism of rate-determining proton transfer.

In aqueous acid, diazoalkanes are hydrolyzed by a mechanism consisting of rate-determining proton transfer followed by rapid bimolecular displacement of the diazonium group (A-S_E2) [2] [3]. It needs the presence of a base to make the proton transfer reversible, for instance OH^- in the case of diazomethane [4] (eq. 1).

$$\text{R-CHN}_2 \underset{\text{base}}{\overset{H^+}{\rightleftarrows}} \text{R-CH}_2\text{N}_2^+ \xrightarrow{H_2O} \text{R-CH}_2\text{OH} + \text{N}_2 + \text{H}^+ \qquad (1)$$

If the primary diazoalkane is deactivated by an electron attracting group, typically R−CO− or ROOC−, protonation is slowed down and deprotonation by water molecules becomes important; the mechanism changes to preequilibrium protonation followed by rate-determining bimolecular displacement (*A*2) [5] [3]. If, however, the *a*-diazoketone or *a*-diazoester is secondary ($R-CO-CN_2-R'$ or $ROOC-CN_2-R'$), the normal mechanism A-S_E2 is found [1], and it needs bases stronger than water to get efficient deprotonation. Electron attracting aryl groups, as in p-$NO_2-C_6H_4-CHN_2$, do not suffice to shift the mechanism from A-S_E2 to *A*2 in primary diazo compounds [6]. We were interested to see whether other electron attracting groups, particularly F_3C-, can bring about this change of mechanism. We therefore investigated the behaviour of the primary trifluoromethyl-diazoalkane **1**[2]); for comparison some experiments with two secondary trifluoromethyl-diazoalkanes **2** and **3** were included.

CF_3CHN_2	$CF_3-CN_2-CH_3$	$CF_3-CN_2-CF_3$	$CF_3CH_2N_2^+$
1	**2**	**3**	**4**

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[1]) Taken from the doctoral thesis by *J. Lenoir*, Lausanne 1968. Preliminary publication: [1].

[2]) *Roedig* [7] has reported that trichloromethyl-diazomethane cannot be prepared by nitrosation of the corresponding amine; we can confirm his finding of elimination reactions and were not successful in our attempts to prepare this compound by other methods.

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Syntheses. - Trifluoro-diazoethane **1** [8] was obtained by diazotation of 2,2,2-trifluoro-ethylamine [8] [9]; it is a yellow gas of b.p. 13° [8], which we characterized by the formation of a phosphazine derivative. 1,1,1-Trifluoro-2-diazo-propane (**2**) [10] was prepared by the oxidation with $Pb(OAc)_4$ [11] of trifluoroacetone-hydrazone [10]; because of the explosive character of the low-boiling liquid [10] it was stored in solution. 1,1,1,3,3,3-Hexafluoro-2-diazo-propane (**3**) [12] [13], a yellow gas of b.p. 14°, was obtained by diazotation [12] of the corresponding amine [12] [14].

Hydrolyses. - In aqueous acid **1** and **2** are rapidly hydrolyzed. The volume of N_2 liberated by **1** was measured to be 98.5% of the expected quantity. The product formed in aqueous solution, CF_3CH_2OH, was identified by gas chromatography; several quantitative determinations by the same technique showed yields of 91-96%. No other volatile organic products could be detected. Solutions of **2** in aqueous dioxane typically led to 85-90% of the expected volume of N_2; the loss might be due to aging of stored solutions.

Kinetics of hydrolysis. - As preliminary experiments showed that the hydrolysis of **1** and **2** in water was too rapid to apply classical techniques (half-lives typically < 1 min.), we modified the normal reaction conditions in the following way: **1** was mostly studied in dioxane/water 60:40 *(v/v)* at 15.0° in the presence of an excess of acid, the rate being measured by following the volume of N_2 liberated [15]. When experiments had to be done in water, the concentration of acid was in some experiments kept lower than that of **1**. In the absence of nucleophiles stronger than H_2O the catalytic proton is regenerated in the course of the reaction (eq. 1); in this case we used polarography at a fixed potential [16] to follow the disappearance of the starting material.

Compound **2** reacted about 200 times more rapidly than **1**, and was investigated in a restricted number of runs only, employing dioxane/water 60:40 at 0.0° and an excess of **2** over that of the acid.

Unless mentioned otherwise, individual runs were 90-95% first order; the $k_{obs.}$ were reproducible to at least ±5%.

Varying $[HClO_4]$ in *aqueous dioxane* over ten-fold at constant ionic strength gave a linear increase in $k_{obs.}$ *(Fig. 1)*. The second order rate constant was $k_2 = k_{obs.}/[H^+] = 0.188 \pm 0.002\,\text{M}^{-1}\,s^{-1}$ (dioxane/water 60:40; 15.0°; $\mu = 0.10$). Added $NaClO_4$ showed a positive salt effect, an increase of μ from 0.01 to 0.1 leading to a *ca.* 30% increase in $k_{obs.}$ *(Table 2)*. Extrapolating to $\mu = 0$ we obtained $k_2 = 0.133 \pm 0.012\,\text{M}^{-1}\,s^{-1}$ (dioxane/water 60:40; 15.0°; $\mu = 0$).

In order to evaluate the influence of strong nucleophiles on the substitution step of the reaction (provided it is rate-determining) rates were measured in the presence of varying amounts of Br^-. The individual runs, however, showed deviation from first order kinetics, presumably due to consumption of protons: if in eq. 1 the nucleophile H_2O is replaced by Br^-, the protons bound in the first step of the reaction are no longer replaced in the second step. Comparing the initial rates only, we found a strong increase in rate over that caused by the $NaClO_4$ salt effect. The effect was, however, not linear in $[Br^-]$, but tended towards a limiting value, which was nearly reached at $[Br^-] \sim 0.1\,\text{M}$ (for $[H^+] = 10^{-2}\,\text{M}$) *(Table 3)*. For lower

[Br^-] we estimate a catalytic second order rate coefficient $k_{Br}\sim 0.05$ M^{-1} s^{-1}. Expressed on a molar basis, Br^- was about 500 times more reactive than H_2O, which shows that there is a rate-determining step in which a nucleophile (Br^- resp. H_2O) is involved. A similar factor was found for the Br^- acceleration of diazoketone hydrolysis [5] [17]; this is in agreement with the *Swain-Scott* relation [18] for a not very highly discriminating substrate.

Experiments with varying buffer concentrations, at constant pH and ionic strength should indicate whether the reaction shows general acid or specific lyonium catalysis. Using a buffer of chloroacetic acid/chloroacetate 1:1 at different dilutions (from 0.025 to 0.10 M; pH* = 3.05), we found a 50% increase in rate upon 4-fold increase of buffer concentration *(Table 4)*. The same was found for a parallel series with 2:1 buffer ratio (pH* = 2.8). In neither series was a deviation from linearity of $k_{\mathrm{obs.}}$/[buffer] observed. This acceleration can be interpreted either as a small general acid catalysis term, or an important positive specific salt effect, or a combination of both.

In order to distinguish between *A*2 and *A*-S_E2 mechanisms, we determined the kinetic solvent isotope effect $k^{\mathrm{H}}/k^{\mathrm{D}}$ by measuring the hydrolysis in 0.025 M $HClO_4$ and $DClO_4$, respectively, under identical conditions (dioxane/water 60:40; no added neutral salt; 15.0°; $\mu = 0.025$). A kinetic solvent isotope effect $k^{\mathrm{H}}/k^{\mathrm{D}} = 0.25$ was calculated from $k^{\mathrm{H}}_{\mathrm{obs.}} = 3.59 \cdot 10^{-3}$ s^{-1} and $k^{\mathrm{D}}_{\mathrm{obs.}} = 14.3 \cdot 10^{-3}$ s^{-1} (each value represents the mean of two determinations).

We determined *(Table 5)* the activation parameters by rate measurements at 0.0°, 7.5° and 15.0° in 0.1 M $HClO_4$ (dioxane/water 60:40): $\Delta H^{\neq} = 14.0 \pm 0.2$ kcal/mol and $\Delta S^{\neq} = -19.9 \pm 1$ e.u.

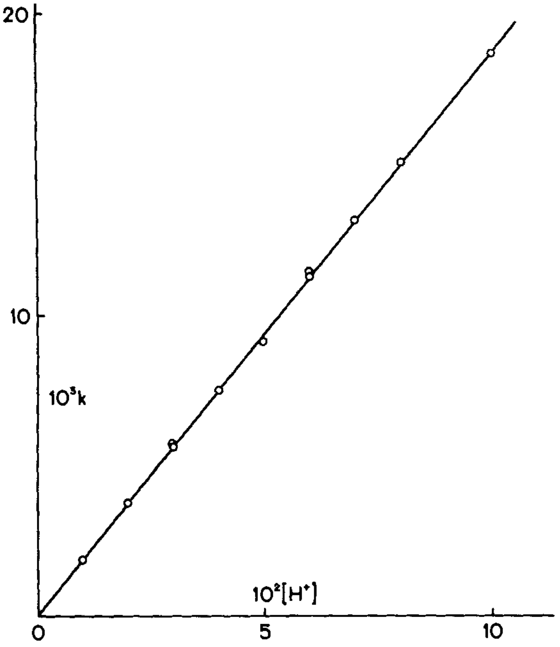


Fig. 1. *Hydrolysis rates of* **1**: *variation of* $k_{obs.}$ *in function of* $[H^+]$ (dioxane/water 60:40; 15.0°; $\mu = 0.10$; *cf. Table 1*)

As mentioned before the reaction rates were considerably higher in *aqueous solution* than in dioxane/water, necessitating a change of technique. With *ca.* 10^{-3} M $HClO_4$ we found $k_2 = 10.3 \pm 0.2$ M^{-1} s^{-1} (15.0°; H_2O; $\mu = 0.1$; *Table 6*); this corresponds to a 55-fold increase of rate over that in dioxane/water (under analogous conditions). Variation of [H^+] was not feasible at such low concentrations of $HClO_4$ and in the presence of an excess of **1**; using standard phthalic acid/hydrogen phthalate buffers (modified by replacing HCl by $HClO_4$ in order to avoid an additional nucleophile) at several pH values between 3.0 and 4.0, good proportionality between [H^+] (taken from measured pH values) and $k_{\text{obs.}}$ can be observed, the straight line passing very nearly through the origin *(Fig. 2)*; $k_2 = k_{\text{obs.}}/[H^+] = 12.5 \pm 0.2$ M^{-1} s^{-1} was evaluated from the slope, this value being slightly higher than that in $HClO_4$ (the difference might be due to specific salt and/or nucleophile effects).

In order to detect general acid catalysis, a series of hydrolyses were run in phthalate buffers at (nearly) constant pH (by dilution) and at constant μ. After corrections for small measured variations of [H^+], k_2 was only slightly dependent upon the buffer concentration *(Table 8)*. Extrapolating to [buffer] = 0 we found $k_2 = 10.2 \pm 0.2$ M^{-1} s^{-1}, in agreement with the values found in $HClO_4$ and in buffer by variation of pH; this means that, if there is a general acid catalysis term, it is again quite small.

The activation parameters for reaction in aqueous solution by measuring at 10.0°, 20.1° and 29.7° *(Table 9)* have the following values: $\Delta H^{\ddagger} = 13.8 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = -21.7 \pm 1$ e.u. for [$HClO_4$] $= 1.0 \cdot 10^{-3}$ M and $\mu = 0.1$. Using the values of the two series (*Tables 5* and *9*) (interpolated for a common temperature and corrected

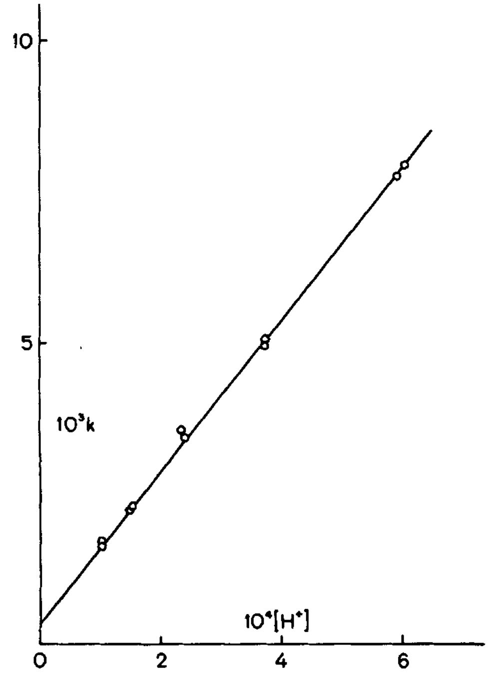
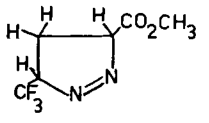


Fig. 2. *Hydrolysis rates of* **1** *in aqueous buffer solutions* (phthalic acid/phthalate) *of different pH values* ([**1**]$_{\text{init.}}$ $= 2.0 \cdot 10^{-3}$ M; t = 15.0°; $\mu = 0.10$; *Table 7*)

for the same acid concentration) we find again that in water the reaction is 56 times more rapid than in dioxane-water.

Mohrig & Keegstra mentioned [19], without giving details, that complete H, D-exchange occurs during the hydrolysis of **1** in D_2O. The reversibility of protonation is confirmed qualitatively by the mode of formation of **1** which involves diazotation of $CF_3CH_2NH_2$ and immediate deprotonation of the intermediate $CF_3CH_2N_2^+$ (**4**). In order to establish whether the protonation of **1** is fully reversible, **1** was treated with D_2O under the conditions of hydrolysis (dioxane/D_2O 60:40; 0.0°; $[DClO_4] = 10^{-2}$M) and unreacted **1** was isolated after about one half-live of the reaction. The product showed a weak band at 2300 cm^{-1} in the IR. spectrum indicative of a C–D-bond. Mass spectrometry showed considerable H, D-exchange; the results were, however, not quantitatively reproducible. Similar difficulties were found when we tried to follow the exchange in the NMR.

For this reason unreacted **1** was transformed into a stable derivative, incapable of further exchange, using the reaction with methyl acrylate [20]. The first product formed at low temperature is 3-methoxycarbonyl-5-trifluoromethyl-pyrazoline-1 (**5**), which was not isolated in pure form because it is easily rearranged thermally to the more stable, crystalline 3-methoxycarbonyl-5-trifluoromethyl-pyrazoline-2 (**6**). Compound **6** is characterized by an IR. band at 3410 cm^{-1} for N–H and an NMR. signal corresponding to NH at 6.9 ppm. That the proton at C(5) does not take part in the rearrangement was shown by reaction of **1**-d with methyl acrylate and isolation of **6**-d, which completely lacked the NMR. signal of H–C(5) at 4.6 ppm without any randomization of deuterium. For kinetic runs, deuterium analysis by mass spectrometry was preferred. Preliminary results showed that the peaks at *m/z* 197/196 (molecular mass) and 128/127 ($M^+ - CF_3$) gave reproducible mass ratios; these principal peaks were identified by high resolution mass spectrometry.



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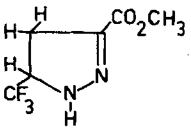

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For reasons of comparison, the exchange experiments were carried out under conditions comparable to those of hydrolysis, with the exception of using a lower acid concentration: $[DClO_4] = 1.0 \cdot 10^{-3}$M; dioxane/$D_2O$ 60:40; $\mu = 0.10$ ($NaClO_4$). After different time intervals samples were withdrawn, transformed into **6** and analyzed by mass spectrometry. At 15.0°, when the hydrolysis is expected to have a half-life of 13.8 min., the exchange reaction turned out to be too rapid to follow. In a run at 0.0°±0.05° *(Table 10)* we found $k_{obs.}^{exchange} = ca.\ 1.5 \cdot 10^{-2}\ s^{-1}$, which gives a second order rate constant $k_2^{exchange} = ca.\ 15\,M^{-1}\,s^{-1}$.

In order to supplement our measurements with **1**, some rates of hydrolysis of **2** were determined. Compound **2** reacted much more rapidly than **1**: in dioxane/water 60:40 the temperature had to be lowered to 0.0° and the acid concentration to $1.01 \cdot 10^{-3}$M in order to follow the reaction by N_2-evolution. The individual reactions were first order for over 90%. By dividing $k_{obs.}$ by $[H^+]$ the second order rate constant

$k_2^{\mathrm{H}} = 9.64\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ (0.0°) was obtained; in dioxane/D_2O the result was $k_2^{\mathrm{D}} = 5.75\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$. The kinetic solvent isotope effect is $k^{\mathrm{H}}/k^{\mathrm{D}} = 1.67$ *(Table 11).*

On the other hand $CF_3{-}CN_2{-}CF_3$ (**3**), doubly deactivated, was found to undergo hydrolysis too sluggishly (half-life about 10 h at 20° in 5 N acid); this behaviour is comparable to that of 2-diazo-1,3-diketones, which are quite stable towards concentrated acid [21]. However, in a super-acid **3** is completely protonated on the carbon atom, and the diazonium ion formed undergoes a displacement reaction [19], whereas diazo-carbonyl compounds are protonated on the oxygen atom [22] (FSO_3H or FSO_3H/SbF_5, respectively).

Discussion. – The kinetic isotope effect of $k^{\mathrm{H}}/k^{\mathrm{D}} = 0.25$ found for **1** is typical of a preequilibrium protonation reaction (*cf.* ethyl diazoacetate $k^{\mathrm{H}}/k^{\mathrm{D}} = 0.34$ [23]). This is confirmed by the finding of rapid H,D-exchange. *Mohrig & Keegstra* [19] had shown the existence of the diazonium ion $CF_3CH_2N_2^+$ **4** at –60° in FSO_3H; in the more nucleophilic aqueous dioxane at 0° and 15°, **4** is formed as a short-lived intermediate during hydrolysis and exchange. Its decomposition is a bimolecular process, as evidenced by the high rate increase caused by a strong nucleophile. The effects found in buffer solutions are not in contradiction with this explanation: provided the (formal) term of general acid catalysis is real, it might well be due to specific lyonium ion catalysis combined with the action of the buffer base as a nucleophile. The kinetic system corresponds to a typical *A* 2 mechanism, as

$$\underset{\mathbf{1}}{CF_3CHN_2} \underset{k_{-\mathrm{p}}}{\overset{k_{\mathrm{p}}}{\rightleftarrows}} \underset{\mathbf{4}}{CF_3CH_2N_2^+} \xrightarrow{k_{\mathrm{d}}} CF_3CH_2OH + H^+ + N_2 \qquad (2)$$

observed for other strongly deactivated primary diazoalkanes. We have to conclude that F_3C- is a strong enough electron withdrawing group to transform the normal *A*-S_E2 mechanism of diazoalkane hydrolysis into *A*2, as is the case with carbonyl, ester, and sulfonyl groups [2], but not with *p*-nitrophenyl [6].

On the other hand the secondary trifluoro-diazoalkane **2** is hydrolyzed by an *A*-S_E2 mechanism, as is evidenced by the normal (though low) isotope effect $k^{\mathrm{H}}/k^{\mathrm{D}} = 1.66$; this result is comparable to that found with the much slower reacting $Ar{-}CN_2{-}CF_3$, which shows $k^{\mathrm{H}}/k^{\mathrm{D}}$ between 2.02 and 2.13, depending upon the substituent in Ar [24]. An analogous situation is found with carbonyl- and ester-deactivated diazoalkanes with $k^{\mathrm{H}}/k^{\mathrm{D}}$ values typically about 2.5 [3].

In the case of **2** (mechanism *A*-S_E2) the over-all velocity constant is that of the transfer of a proton or deuteron, respectively: $k_2^{\mathrm{D}} = k_{\mathrm{p}}^{\mathrm{D}} = 5.7\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ (dioxane/water; 0.0°). For **1** the latter constant can be approximated by H,D-exchange: Assuming that, as usual, the intermediate diazonium ion **4** is not accumulated, but that the rate of deprotonation ($k_{-\mathrm{p}}$) is much greater than that of protonation (k_{p}), the observed rate is (approximately) that of deuteration of **1**: $k_2^{\mathrm{exchange}} \sim k_{\mathrm{p}}^{\mathrm{D}} = ca.\ 15\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ (dioxane/water; 0.0°).

The comparison shows that for **1** and **2** the rates of deuteration (and those of protonation, too) are of the same order of magnitude. This is in accord with results in the diazoketone series (water; 0°): $MeCO{-}CHN_2$ $k_{\mathrm{p}}^{\mathrm{D}} = 19.0 \cdot 10^{-2}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ [25]; $MeCO{-}CN_2{-}Me_2$ $k_{\mathrm{p}}^{\mathrm{D}} = 2.1 \cdot 10^{-2}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ (estimated from $k_{\mathrm{p}}^{\mathrm{H}} = 5.5 \cdot 10^{-2}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ [25], obtained by extrapolation to 0° [26], with $k^{\mathrm{H}}/k^{\mathrm{D}} = 2.6$ [26]).

As mentioned above the rate of deuteration for **1** is $k_p^D = ca.\ 15\,\text{M}^{-1}\,\text{s}^{-1}$. Under the same conditions (dioxane/D_2O 60:40; 0.0°) the over-all rate constant for hydrolysis would be $k_2^D = 0.18\,\text{M}^{-1}\,\text{s}^{-1}$ (from k_2^H at 0° and $k^H/k^D = 0.25$). Taking into account that the over-all rate constant $k_2^D = k_p^D \cdot k_d^D/k_{-p}^D$, we find $k_p^D/k_2^D = k_{-p}^D/k_d^D = 15{:}0.18 = ca.\ 80$; this is the ratio of the back to the forward reaction of the deuterated diazonium ion **4**-d (eq. 2). For the same system with H^+ instead of D^+, the ratio k_{-p}^H/k_d^H of the back to the forward reaction of **4** might be 2 to 4 times larger, as estimated on the basis of the isotope effects upon the individual steps. This means that, for the protonated as for the deuterated diazonium ion, the ratio of the back to the forward reaction is of the order 10^2. - In the analogous case of diazoacetone in which we evaluated 4 different exchange reactions (H → D; D → H; T → H; T → D), it could be shown [25] that the isotope effect on deprotonation: $k_{-p}^H/k_{-p}^D = 3.7$ contributed must to the over-all isotope effect. The ratio of the back to the forward reaction of the diazonium ions k_{-p}/k_d was 51 in D_2O and 164 in H_2O, *i.e.* again of the order of magnitude 10^2.

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Experimental Part

General remarks: see [17]. RT. = room temperature. Purification of solvents and preparation of solutions for kinetics: [6]. Mass spectra at high resolution: Institut de chimie physique, EPFL.

Trifluoro-diazoethane (**1**) [8]. To a stirred solution of 0.68 g (0.5 mmol) of 1,1,1-trifluoroethylamine · HCl [9] in 5 ml water and 10 ml dibutyl ether at 0° were added 0.38 g (0.53 mmol) of $NaNO_2$. After 5 min the organic layer was replaced by fresh solvent and the extraction repeated 3 times after prolonged intervals. The collected extracts were washed with aqueous hydrogencarbonate solution, and dried over $MgSO_4$; **1** was distilled under vacuum into a trap cooled by liquid air, and purified by two redistillations (yield: 70-75%). For storage it was distilled into dry dioxane or CCl_4; the concentration in solution was determined by weight; freshly prepared solutions liberated with acid 98.5% of the expected volume of N_2. - IR. (CCl_4): 3150, 2980, 2120, 1390. - NMR. (CCl_4): 4.38 (*qa*, $J_{HF} = 4$ Hz). - MS.: 110 (100%), 91 (18), 82 (8.6), 69 (33), 63 (71).

Trifluorodiazoethane-d (**1**-d) has been prepared by nitrosating 5 mmol of trifluoroethylamine · HCl with 5.5 mmol of $NaNO_2$ in 5 ml of D_2O at RT. The liberated **1**-d was condensed at −180°, then distilled into 4 ml of dry dioxane. When it was necessary to remove residual H, this solution was added to 6 ml of 0.01 N $DClO_4$ in D_2O and after some seconds extracted with petroleum ether; **1**-d was isolated by distillation. - MS.: 111 (100%), 92 (15), 83 (10), 69 (42), 64 (66).

Triphenylphosphazine of **1**. 0.70 g Triphenylphosphine in 9 ml of dry ether and 2 ml of a 1.2 M solution (titrated with benzoic acid) of **1** in dioxane were kept 15 h in the dark at RT. The solvent was evaporated under vacuum; the residue was recrystallized from petroleum ether: 0.67 g (75%), m.p. 97-98°.

$C_{20}H_{16}F_3N_2P$ (372.3) Calc. C 64.52 H 4.33 N 7.52% Found C 64.66 H 4.46 N 7.66%

1,1,1-Trifluoro-2-diazopropane (**2**) [10]. A mixture of 0.63 g of 1,1,1-trifluoroacetone hydrazone (5.0 mmol) [10] and 2.33 g of $Pb(OAc)_4$ (5.3 mmol) [11] in 20 ml of dibutyl ether were reacted with stirring 45 min at 0°. After filtration of the solution, **2** was distilled under vacuum into a cooled trap (liquid air), then redistilled into a weighed quantity of dry dioxane (or CCl_4) cooled to −180°. Yield: about 65% (by weight). Even when kept in dark at −20°, dioxane solutions of **2** slowly decompose (loss about 5% per day), as judged by the volume of N_2 evolved during acid hydrolysis.

1,1,1,3,3,3-Hexafluoro-diazopropane (**3**) [12] [13]. To 1.02 g of hexafluoro-isopropylamine · HCl [14] (5.0 mmol) in 5 ml water and 10 ml dibutyl ether [8] at 0° were added 0.69 g of $NaNO_2$ (10 mmol) and 2 ml of N $HClO_4$. After 10 min stirring at 0° the organic layer was replaced by fresh dibutyl ether; 2 ml acid were added; the operation was repeated a third time, with prolonged standing. The united organic phases were dried over $MgSO_4$; **3** was distilled under slightly diminished pressure and collected in a cool trap containing dioxane. - IR. (CCl_4): 2140 (diazo).

3-Methoxycarbonyl-5-trifluoromethyl-pyrazoline-2 (**6**) [20]. A solution of **1** in petroleum ether (prepared by nitrosating 5.0 mmol of amine under petroleum ether) mixed with 2.0 ml of methyl acrylate (4-fold excess) was allowed to react in the dark at RT. After 30 min the solution was dried over $MgSO_4$; the volatile constituents were distilled at 20°/0.01 Torr, the residue refluxed for 1 h in THF. After adding the same volume of petroleum ether and cooling, **6** crystallized; after recrystallisation from methanol/petroleum ether m.p. 110-110.5° (litt. [20] m.p. 109-109.5°). - IR. ($CHCl_3$): 3410 (N-H), 3050, 3000, 2960 (C-H), 1720 (conj. ester), 1590 (conj. C=N). - NMR. ($CDCl_3$): 6.9 (large, 1 H, NH); 4.64 (*m*, 1 H, H-C(5)); 3.98 (*s*, 3 H, CH_3); 3.39 and 3.19 (2 *d*, each 1 H, CH_2). - MS.: 196 (22%), 165 (23), 137 (13), 127 (28), 96 (11), 95 (100%). - High resolution MS.: 127.1205 ($C_5H_7N_2O_2$, calc. 127.1201); 95.0247 ($C_4H_3N_2O$, calc. 95.0245); 28.0188 (CH_2N, calc. 28.0187).

The corresponding 5-deuterated pyrazoline (**6**-d) was prepared from trifluorodiazoethane-d as described above. In the NMR. spectrum the multiplet at $\delta = 4.64$ had disappeared. - MS.: 197 (14%), 166 (16), 138 (20), 128 (22), 96 (100), 95 (18). - High resolution MS.: 128.1200 ($C_5H_6DN_2O_2$, calc. 128.1201); 96.0310 ($C_4H_2DN_2O$, calc. 96.0319).

When the reaction of **1** in dioxane with methyl acrylate in ether was conducted at low temperature without heating in THF, the distillate (0.01 Torr), after elimination of the solvent consisted of crystalline **6** and an oil. The latter showed (accompanied by signals of **6**): IR. ($CHCl_3$) 1740 (C=O, non-conj. ester), 1560 (cyclic N=N). - NMR. ($CDCl_3$): 5.67 (*m*, 1 H, H-C(3)); 5.20 (*m*, 1 H, H-C(5)); 3.92 (*s*, 3 H, CH_3); 2.17 (*m*, 2 H, CH_2). The spectral data are consistent with the formula **5** of a pyrazoline-1; upon heating or standing overnight at RT. this compound is transformed into **6**.

Hydrolysis: product analysis. - A mixture of 70 mg of $HClO_4$ 70% (0.50 mmol), 2.0 ml of water and 1.0 ml of dioxane were cooled to −180°. 2.00 ml of a dioxane solution containing 2.73 mmol of **1** (±2%, determined by azotometry) were added and again cooled to −180°; the flask was evacuated to 10 Torr and warmed up. After 4 h at RT. the mixture was neutralized by 50 mg (0.50 mmol) of $KHCO_3$; the volatile constituents were sublimed at 10^{-4} Torr, condensing the product at −180°: 5.11 g; samples of 40 µl were injected into the gas chromatograph. 'ASA 161' (250 ml 'terra silicea *Merck* 9696' plus 20 ml of di-(2-ethyl-hexyl)-sebacate) at 100° was satisfactory to separate water (retention time 1.75 min), CF_3CH_2OH (5.35 min) and dioxane (9.9 min). Quantitative determinations of CF_3CH_2OH in the distillate were accomplished after calibration with blanks: error *ca.* ±4-5%. In the typical run described we found that 5.11 g of sublimate contained 5.12% of $CF_3CH_2OH = 262$ mg, corresponding to a yield of 96% (based on N_2-volume liberated during a parallel hydrolysis run).

Table 1. *Hydrolysis rates of* **1** *as function of* *[H+]* (dioxane/water 60:40; t = 15.00+0.03°; $\mu = 0.10$; $[\mathbf{1}]_{init.}$ *ca.* $2 \cdot 10^{-3}$ M)

$[HClO_4]$ (mol · l^{-1})	$[NaClO_4]$ (mol · l^{-4})	$10^3 \cdot k_{obs.}$ (s^{-1})
0.01	0.09	1.90
0.02	0.08	3.78
0.03	0.07	5.63
0.03	0.07	5.73
0.04	0.06	7.51
0.05	0.05	9.14
0.06	0.04	11.5
0.06	0.04	11.3
0.07	0.03	13.2
0.08	0.02	15.1
0.10	0.00	18.7

Table 2. *Hydrolysis rates of* **1** *as function of* μ ($[H^+] = 1.07 \cdot 10^{-2}$ M; dioxane/water 60:40; t = 15.0°; $[\mathbf{1}]_{init.}$ *ca.* $2 \cdot 10^{-3}$ M)

$[NaClO_4]$	$10^2 \cdot \mu$	$10^3 \cdot k_{obs.}$ (s^{-1})
0.00	1.07	1.47
0.01	2.07	1.58
0.02	3.07	1.59
0.03	4.07	1.66
0.04	5.07	1.68
0.05	6.07	1.77
0.06	7.07	1.81
0.07	8.07	1.84
0.08	9.07	1.94
0.09	10.07	1.98

Table 3. *Hydrolysis rates of* **1***: influence of added* Br^- ($[H^+] = 1.0 \cdot 10^{-2}$ M; dioxane/water 60:40; t = 15.0°; $[\mathbf{1}]_{init.}$ *ca.* $2 \cdot 10^{-3}$ M)

[NaBr]	μ	$10^3 \cdot k_{obs.}$[a]) (s^{-1})	[NaBr]	μ	$10^3 \cdot k_{obs.}$[a]) (s^{-1})
0.00	0.01	1.5	0.05	0.06	3.5
0.01	0.02	2.2	0.06	0.07	3.5
0.02	0.03	2.5	0.07	0.08	3.7
0.03	0.04	3.0	0.08	0.09	3.8
0.04	0.05	3.1	0.09	0.10	4.2

[a]) Initial rates.

Table 4. *Hydrolysis rates of* **1** *in buffer of* $CHCl_2COOH/CHCl_2COONa$ *1:1 and 2:1 of variable concentration* (dioxane/water 60:40; t = 15.0°; $\mu = 0.10$. $[\mathbf{1}]_{init.}$ *ca.* $2 \cdot 10^{-3}$ M)

[HA] ($mol \cdot l^{-1}$)	$[A^-]$ ($mol \cdot l^{-1}$)	$[NaClO_4]$ ($mol \cdot l^{-1}$)	$pH_{init.}$	$10^4 \cdot k_{obs.}$[a]) (s^{-1})
0.100	0.100	0.00	3.00	3.83
0.100	0.100	0.00	3.09	3.66
0.100	0.100	0.00	-	3.68
0.075	0.075	0.025	-	3.12
0.050	0.050	0.050	3.10	2.98
0.050	0.050	0.050	3.10	3.05
0.050	0.050	0.050	-	2.66
0.025	0.025	0.075	3.04	2.14
0.025	0.025	0.075	3.06	2.33
0.200	0.100	0.00	2.78	7.36
0.100	0.050	0.050	2.83	5.57
0.050	0.025	0.075	2.85	4.47

[a]) The reactions were linear over at least 2 half-lives.

Table 5. *Hydrolysis rates of* **1** *as function of the temperature* ($[HClO_4] = 0.1$ M; dioxane/water 60:40; $\mu = 0.1$; $[\mathbf{1}]_{init.}$ *ca.* $2 \cdot 10^{-3}$ M)

T (K)	$10^3 \cdot k_{obs.}$ (s^{-1})	T (K)	$10^3 \cdot k_{obs.}$ (s^{-1})	T (K)	$10^3 \cdot k_{obs.}$ (s^{-1})
273.15	4.69	280.65	9.03	288.15	17.50
273.11	4.58	280.65	9.38	288.15	17.46
273.07	4.62	280.65	9.39	288.15	17.95
273.07	4.58	280.63	9.37	288.15	17.74
273.07	4.55	280.65	9.48	288.15	18.12

Table 6. *Hydrolysis rates of* **1** *in water* ($[HClO_4] = 1.0 \cdot 10^{-3}$ M; $[NaClO_4] = 99 \cdot 10^{-3}$ M; $[\mathbf{1}]_{init.}$ *ca.* $2 \cdot 10^{-3}$ M; t = 15.0°; polarography)

pH measured	$10^4\,[H^+]$ ($mol \cdot l^{-1}$)	$10^3 \cdot k_{obs.}$ (s^{-1})	k_2 ($M^{-1}\,s^{-1}$)
3.13	7.42	7.74	10.42
3.09	8.12	8.43	10.38
3.09	8.12	8.22	10.12
3.08	8.31	8.54	10.28

Kinetics. - a) *By following the volume of N_2 at constant pressure and temperature;* apparatus: see [15]. In a typical experiment (0.10N $HClO_4$), a mixture of 12.50 ml of 0.20N $HClO_4$ in dioxane/water 60:40 *(v/v)*, 11.67 ml of dioxane/water 60:40 and 0.33 ml of water were thermostated inside the apparatus at 15.00±0.02° while bubbling N_2 *(puriss.)* throught the solution; in a separate part of the apparatus, 0.50 ml of a dioxane solution containing about 0.5 mmol of **1** were thermostated. After equilibration of pressure and stopping of the N_2-flow the run was started by mixing the two solutions. The volume of N_2 liberated was measured at short time intervals (10-15 s), after equilibration of pressure.

b) *By polarography at fixed tension* [16]: apparatus *Metrohm* E261, equipped with a pulsor (7 cps.) for rapid cadence of mercury drops. Reference electrode Ag/AgCl sat. The solutions, made up in the usual way and containing 0.1% of Triton X to suppress maxima, were thermostated under 99.999% N_2 and agitated magnetically. The tension was fixed at -1.18 V, slightly below the half-wave potential determined in preliminary tests ($E_{1/2} = -1.14$ V). The time scale was marked during the progress of

Table 7. *Hydrolysis rates of* **1** *in 10.0 ml phthalic acid-hydrogen phthalate buffer; prepared by mixing 50.0 ml of 0.10*M *potassium hydrogen phthalate with X ml of 0.10*N *perchloric acid* [29] (0.06 ml of a 0.34M dioxane solution of **1**, *i.e.* $[\mathbf{1}]_{init.} = 2.0 \cdot 10^{-3}$M; E = -1.15 V; t = 15.0°; polarography)

X (ml)	$10^2 \cdot \mu$	pH measured	10^4 [H+]	$10^3 \cdot k_{obs.}$ (s^{-1})
15.7	7.70	3.23	5.90	7.78
15.7	7.70	3.22	6.02	7.94
10.4	8.38	3.43	3.72	5.08
10.4	8.38	3.43	3.72	4.94
6.3	9.02	3.62	2.40	3.42
6.3	9.02	3.63	2.35	3.55
2.9	9.68	3.82	1.51	2.30
2.9	9.68	3.83	1.48	2.21
0.1	10.35	3.99	1.02	1.71
0.1	10.35	3.99	1.02	1.63

Table 8. *Hydrolysis rates of* **1** *in aqueous phthalic acid-hydrogen phthalate buffers at (nearly) constant pH:* reaction mixtures obtained by mixing X ml of a buffer solution (from 50.0 ml of 0.10M potassium hydrogen phthalate and 22.3 ml of 0.10M perchloric acid) with Y ml of 0.10N $NaClO_4$ solution; $[\mathbf{1}]_{init.} = 2.0 \cdot 10^{-3}$M; at $[H^+] = 3.0 \cdot 10^{-3}$ the ratio $[H_2A_2]$: $[HA_2^-] = 0.77$; E = -1.15 V; $\mu = 0.1$; t = 15.0°; polarography)

X (ml)	Y (ml)	pH meas.	10^3 [H+]	10^2 [H_2A_2]	10^2 [HA_2^-]	$10^3 k_{obs.}$ (s^{-1})	$10^3 k_{obs.}^{corr.}$ [a]
10.0	0.0	3.01	0.98	3.00	3.90	11.7	11.9
10.0	0.0	3.01	0.98	3.00	3.90	11.9	12.1
8.0	2.0	3.00	1.00	2.40	3.12	11.4	11.4
5.0	5.0	3.00	1.00	1.50	1.95	11.6	11.6
5.0	5.0	3.00	1.00	1.50	1.95	11.5	11.5
5.0	5.0	3.00	1.00	1.50	1.95	11.4	11.4
4.0	6.0	3.00	1.00	1.20	1.56	11.4	11.4
4.0	6.0	3.00	1.00	1.20	1.56	11.4	11.4
3.0	7.0	3.01	0.98	0.90	1.18	10.9	11.1
2.0	8.0	3.05	0.89	0.53	0.85	9.9	11.1
2.0	8.0	3.05	0.89	0.53	0.85	9.3	10.4
2.0	8.0	3.05	0.89	0.53	0.85	8.9	10.0
1.0	9.0	3.12	0.76	0.25	0.47	7.3	9.6
1.0	9.0	3.13	0.74	0.24	0.45	7.6	10.3

[a] Corrected for deviation from $[H^+] = 1.0 \cdot 10^{-3}$.

the recorder paper. The smooth curves obtained could be evaluated directly. In a typical run, 0.020 ml of a *ca.* 0.2M solution of **1** in methanol were added to 20.0 ml of aqueous buffer solution at 15.00±0.05°. As the initial concentration of **1** was not known exactly, the velocity constants were evaluated by the *Guggenheim* method [27].

Hydrogen exchange. - A mixture of 13.38 ml of dioxane/D_2O 60:40 *(v/v)* (D_2O 99.5%), 0.62 ml of D_2O and 10.0 ml of a dioxane/D_2O 6:4 solution $2.5 \cdot 10^{-3}$M in DCl_4 and 0.274M in $NaClO_4$ were thermostated at 0.0°. 1.0 ml of a precooled 0.7M solution of **1** in dry dioxane were rapidly added. After thorough mixing 1 ml samples were rapidly withdrawn at fixed time intervals, with the aid of a pressure device, and directly introduced into test tubes containing 2 ml of petroleum ether. After rapid agitation, *ca.* 2/3 of each organic phase were transferred to another test tube containing each 0.2 ml of freshly distilled methyl acrylate. After 20-30 min of reaction the volatile components were evaporated under vacuum; the oily residue of **5**+**6** crystallized after 15-20 h standing at RT. by forming **6**. After drying at 10^{-3} Torr the crystals were analyzed in a mass spectrometer. To determine the deuterium content after exchange we used the mass ratios 197/196 ($=M^+$) and 128/127 ($=M^+ - CF_3$); in blank runs without D^+ they showed the ratios ($M+1$): M of 7.7% (calc. 7.4%) and 6.4% (calc. 6.3%), respectively. This natural abundance of the higher mass [28] was taken into account in the evaluation of the exchange ratio *(Table 10)*.

Table 9. *Hydrolysis rates of* **1** *in water at various temperatures* ($[HClO_4] = 1.0 \cdot 10^{-3}$M; $[NaClO_4] = 99 \cdot 10^{-3}$M; $[\mathbf{1}]_{init.} = 2.0 \cdot 10^{-3}$M; polarography)

T (K)	$10^3 \cdot k_{obs.}$ [s^{-1}]	T (K)	$10^3 \cdot k_{obs.}$ [s^{-1}]	T (K)	$10^3 \cdot k_{obs.}$ [s^{-1}]
283.20	6.00	293.30	14.6	302.97	30.6
283.20	6.07	293.30	14.4	302.97	29.9
283.20	6.11	293.30	14.8	302.97	29.9
283.20	6.13	293.30	14.5	302.97	29.8
283.20	6.04	293.30	14.4	302.97	30.0
283.20	6.04	293.30	14.4	302.97	29.7
283.20	5.95	293.30	14.3	302.97	30.4

Table 10. *Exchange H–D of* **1** (dioxane/D_2O 60:40; $[DClO_4] = 1.0 \cdot 10^{-3}$M; $[NaClO_4] = 99 \cdot 10^{-3}$M; $D_2O = 99.5\%$; t=0.00±0.05°; determination by mass spectrometry of **6** at masses 197/196 (a) and 128/127 (b))

Time (s)	% D a	% D b	Time (s)	% D a	% D b
95	76.9	77.0	215	91.3	91.2
115	77.9	85.7	275	92.7	93.0
140	86.9	87.3	330	94.1	93.2
175	79.0	-	410	94.1	93.3

Table 11. *Hydrolysis rates of* **2**: *kinetic solvent isotope effect* (dioxane/water 60:40; $[\mathbf{2}]_{int.}$ *ca.* $2 \cdot 10^{-3}$M; t=0.00±0.05°)[a])

$10^3 \cdot [HClO_4]$ resp. $[DClO_4]$	$10^3 \cdot k_{obs.}$ (s^{-1})	$10^3 \cdot [HClO_4]$ resp. $[DClO_4]$	$10^3 \cdot k_{obs.}$ (s^{-1})
1.011 (H^+)	9.82	1.006 (D^+)	5.76
1.011 (H^+)	9.68	1.006 (D^+)	5.73
1.011 (H^+)	9.80	1.006 (D^+)	5.84
1.011 (H^+)	9.70		

[a]) Experiments by *G. Diderich*.

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