HYDROLYSIS OF FLUOROALKYL-CONTAINING β-AMINOVINYL KETONES

L. N. Bazhenova, V. I. Filyakova, V. E. Kirichenko, and K. I. Pashkevich

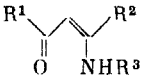
UDC 541.127:542.938:547.447.5'161

The kinetics of hydrolysis of fluoroalkyl-containing β-aminovinyl ketones $R^1C(O)CHC(NHR^3)R^2$, in which the substituents CF_3 and HCF_2CF_2 are in the ketone (R^1) or enamine parts of the molecule (R^2), was studied. In acid (pH < 5) and alkaline (pH > 10) media, they hydrolyze with the formation of the corresponding amines and β-diketones. In an alkaline medium, the β-diketones undergo cleavage to fluorinated acids and methyl ketones. The rate constants of hydrolysis in an acid medium change within a range of four orders, depending on the nature of the substituents. The presence of a fluoroalkyl group at the enamine reaction center increases the hydrolysis rate. In an alkaline medium, the rate constants vary within one order.

β-Aminovinyl ketones, important intermediates in organic synthesis [1, 2], have complexing and extracting properties [2-5]. In the study of these properties questions arise concerning the stability of the compounds in aqueous and aqueous-organic media at various pH values and concerning the effect of the nature and position of the substituents on the direction and rate of hydrolytic cleavage. Data on the hydrolysis of β-aminovinyl ketones are limited [6-9], and many aspects of the mechanism of the reaction and its limiting step remain controversial [6, 8]. For unfluorinated β-aminovinyl ketones, in particular 4-amino-3-penten-2-one, it was shown that the first step of the process is fast (milliseconds) protonation at N, C, or O atoms with the formation of equilibrium structures [6]. There are proofs of the hydrolysis of both O- and C-protonated forms [1, 6, 9, 10]. The limiting step is most often the addition of water to the protonated molecule, but abstraction of an amine can also occur. In [6, 7], the significant role of the structure of the substituent at the C=C bond was noted, but the nature of this effect was not determined. There are no data on the hydrolysis of fluoroalkyl-containing β-aminovinyl ketones.

The purpose of this paper is a study of the kinetics of hydrolysis of regioisomeric fluoroalkyl-containing β-aminovinyl ketones (Table 1) in acid and basic media and determination of the effect of fluorinated as well as alkyl and phenyl substituents on the rate of hydrolysis in relation to their position in the carbonyl or enamine parts of the molecule.

TABLE 1. Spectral Data of Fluoroalkyl-Containing β-Aminovinyl Ketones in 5% Aqueous Ethanol and Hydrolysis Rate Constants



Compound	R^1	R^2	R^3	λ_1, nm	$\varepsilon_1 \cdot 10^4$	λ_2, nm	$\varepsilon_2 \cdot 10^4$	$k \cdot 10^4$, sec^{-1} in 0.1 M HCl (pH 1.1)	$k \cdot 10^4$, sec^{-1} in 0.1 M NaOH (pH 12.7)
(I)	CF_3	Me	H	310	1,79	–	–	38,0	4,6
(II)	CF_3	Ph	H	330	1,98	250	0,80	5,0	1,0
(III)	$H(CF_2)_2$	Me	H	310	1,68	–	–	1,6	1,8
(IV)	$H(CF_2)_2$	Ph	H	335	2,03	250	0,83	0,1	0,4
(V)	$H(CF_2)_2$	Me	Me	318	1,80	–	–	1,5	2,4
(VI)	Me	CF_3	H	293	1,31	–	–	480,0	2,3
(VII)	Ph	CF_3	H	322	1,72	255	0,52	144,0	8,5

Department of Fine Organic Synthesis, Institute of Chemistry, Bashkir Scientific Center, Urals Branch, Academy of Sciences of the USSR, Sverdlovsk. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 664-669, March, 1991. Original article submitted December 3, 1989.

0568-5230/91/4003-0581$12.50

EXPERIMENTAL

The investigated β-aminovinyl ketones were synthesized according to [11, 12], and their structure and purity were confirmed by melting points and data of elemental analysis, IR spectroscopy, and thin-layer chromatography (TLC). The pH of the solutions was determined using an OR-208/1 pH meter with a combined glass electrode, the accuracy of which was monitored with respect to standard buffer solutions. Scanning electronic-absorption spectra were recorded on a Specord UV-VIS spectrophotometer, and quantitative data for calculation of the rate constants were obtained on a VSU2-P spectrophotometer.

Hydrolysis of 1,1,2,2-Tetrafluoro-5-amino-4-hexen-3-one (III) in Acid and Alkaline Media. To 0.5 g (2.7 mmoles) of compound III were added 20 ml of distilled water and 2 ml of concentrated HCl, and the whole was boiled for 3 h until disappearance of the starting (III) (monitored by TLC). We added 0.2 g (11 mmoles) of copper acetate, stirred the whole for 0.5 h, extracted the resulting copper chelate with ether, drove off the ether, and reprecipitated the blue crystals with water from methanol. We obtained 0.58 g (89%) of a Cu^{2+} bis(1,1,2,2-tetrafluoro-3,5-hexadionato) complex with mp 133-134°C [13].

Acid hydrolysis of (V) and (VI) was carried out similarly. In all cases, we recovered chelates of the corresponding β-diketones with copper in >80% yields.

Hydrolysis of (III) in Alkaline Medium. A solution of 5 g (27 mmoles) of (III) in 10 ml of 5% KOH and 10 ml of ethanol was boiled for 8 h until disappearance of the starting (III) (monitored by TLC), and the evolved NH_3 was absorbed by ether saturated with HCl (gas). The NH_4Cl crystals were filtered and dried. We obtained 1.3 g (90%) of NH_4Cl. To the filtrate was added 20 ml of 20% HCl, 2,2,3,3-tetrafluoropropionic acid was extracted with ether, the ether was driven off, and the acid was converted to the methyl ester. We obtained 2.5 g (57%) of methyl 2,2,3,3-tetrafluoropropionic acid with bp 93-94°C [14].

Alkaline hydrolysis of (IV) and (VI) was carried out similarly. We obtained NH_4Cl in >90% yield and methyl esters of the corresponding acids in 52-67% yields. Acetophenone was recovered in 83% yield in the hydrolysis of (IV). In the hydrolysis of (VI), acetone was identified by GLC.

Hydrolysis Kinetics. Hydrolysis was carried out in 5% aqueous ethanol at 20 ± 0.5°C and 28 ± 0.5°C; the pH of the solution was created with 0.1 M HCl and 0.1 M NaOH.

To a solution of the β-aminovinyl ketone in ethanol with concentration $n \cdot 10^{-3}$ M was added a controlled-temperature solution of HCl or NaOH so that the ethanol content in the reaction soluton was 5% and the starting concentration of the β-aminovinyl ketone was $n \cdot 10^{-5}$ M. The solution was rapidly stirred, and its temperature was controlled. Acid hydrolysis was carried out directly in the cuvette or by a sampling method. The absorbance of the corresponding β-aminovinyl ketone at λ_{max} was measured. The resulting β-diketones did not interfere in the determination. In an analysis of the alkaline-hydrolysis products, an equal volume of 1 M NH_4Cl or 1 M HCl was added to the sample before the measurement to suppress the absorption of β-diketones. The kinetic curves were plotted according to the decrease of the absorbance corresponding to the absorption of the β-aminovinyl ketone (the values of λ_{max} and ε are given in Table 1).

The pseudo-first-order reaction rate constants were calculated according to [15] and using an ES-1061 SVM computer.

RESULTS AND DISCUSSION

Preparatively, it was shown that during boiling (0.5-5 h) in a medium of dilute HCl the regioisomeric β-aminovinyl ketones (III)-(VI) form corresponding β-diketones in >80% yield. During prolonged boiling (10-15 h) in 0.05 M KOH in aqueous ethanol or methanol (50 vol. %), the β-aminovinyl ketones gave cleavage products, i.e., fluorinated acids and unfluorinated methyl ketones and amines. Changes did not occur during prolonged holding of β-aminovinyl ketones (I)-(VII) in neutral aqueous-alcoholic media. Thus, regardless of the position of the fluorinated and unfluorinated substituents, their structure, and the presence of a substituent at the N atom in the acid medium, the reaction occurred at the enamine group. Apparently, the reaction also occurs at this same center in an alkaline medium with the intermediate formation of the corresponding β-diketones, undergoing further C–C cleavage. This agrees with the formation of an identical set of hydrolysis products during the hydrolysis of isomeric β-aminovinyl ketones [e.g., (I) and (VI)].

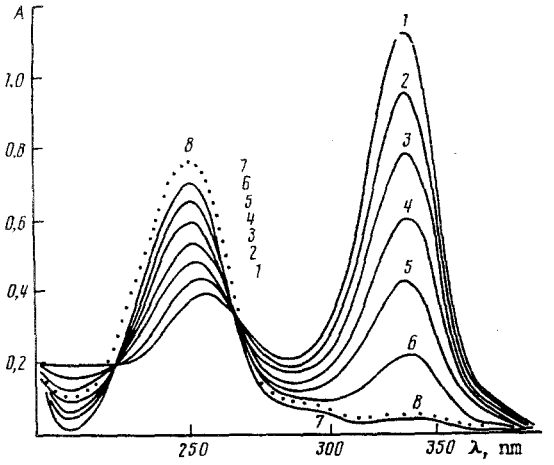


Fig. 1

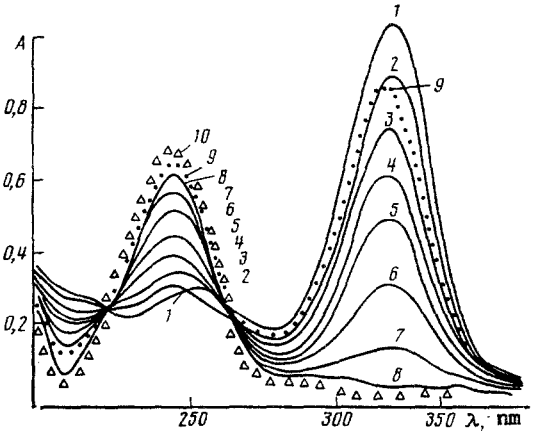
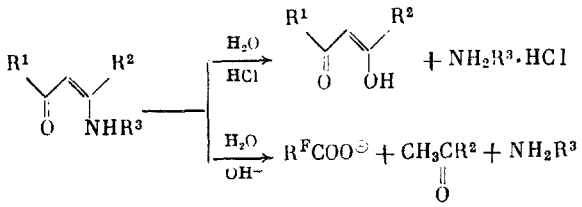


Fig. 2

Fig. 1. Nature of change of spectra during hydrolysis of (II) (pH 1.1, C = $6 \cdot 10^{-5}$ M). Hydrolysis time, min: 1) 2; 2) 8; 3) 15; 4) 25; 5) 37; 6) 60; 7) 115; 8) spectrum of the β-diketone.

Fig. 2. Nature of change of spectra during hydrolysis of (VII) (pH 12.7, C = $6 \cdot 10^{-5}$ M). Hydrolysis time, min: 1) 13; 2) 28; 3) 59; 4) 90; 5) 121; 6) 199; 7) 343; 8) 450; 9, 10) spectra of the β-diketone and acetophenone.



To determine the relation of the occurrence of the process to pH, the hydrolysis of isomeric compounds (I) and (VI) was studied in the pH range 1.1-13.8 at 20°C. To determine the nature of the substituents in the β-aminovinyl ketone molecule, the hydrolysis of compounds (I)-(VII) was studied under the limiting conditions, at pH 1.1 and pH 12.7 and 20°C.

Figures 1 and 2 show the nature of the change of the spectra during hydrolysis in acid and alkaline media, respectively. An analysis of the kinetic curves confirmed that the reaction corresponds to the first order of the β-aminovinyl ketone in all cases. Figure 3 shows the relation of the rate constants of the hydrolysis (k) to the pH of the medium for (I) and (VI). In an acid medium, the relation was rectilinear with an angular coefficient of inclination equal to 1, i.e., at pH < 5 the reaction occurred under acid-hydrolysis conditions. In the alkaline region, the angular coefficient was close to 1, which may be the results of either basic catalysis or participation of the OH^- ion in the limiting step. All compounds were stable at pH 5-10.

On the basis of the data of [6, 7, 10] and the structure of the investigated β-aminovinyl ketones, we can assume that fast protonation is the first hydrolysis step in the acid medium, as in the case of enamines [7] and unfluorinated enamino ketones [6, 10]. Subsequently, reactions of this type occur via steps of addition of water and cleavage of an amine from the intermediate addition product. Any of them can be the limiting step. To obtain information about the limiting reaction step, we analyzed the nature of the effect of substitutents on the reaction rate constant. Acceptor substituents at the reaction center should accelerate the first step because of a decrease of the electron density on the C atom of the azomethine group. Thus, the presence of a strong acceptor, the CF_3 group at the enamine reaction center [of compounds (VI) and (VII)], should lead to an increase of the rate of addition of water in comparison with isomeric compounds (I) and (II), regardless of the participation of the O- or C-protonated form. This corresponds to the data given in Table 1. The lower values of the rate constant k for (II) and (IV), containing a phenyl group at the reaction center with respect to (I) and (III) of analogous structure, but containing a methyl group, are probably due to partial compensation for the positive charge of the azomethine group due to bonding with phenyl. This may also be

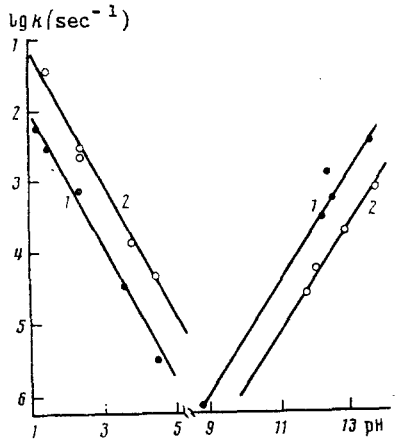
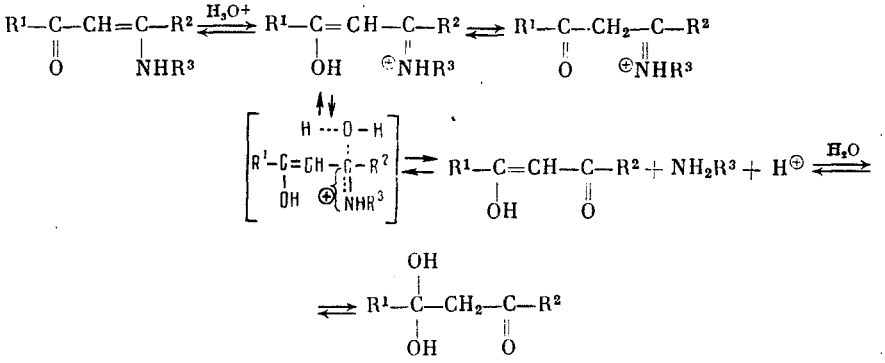


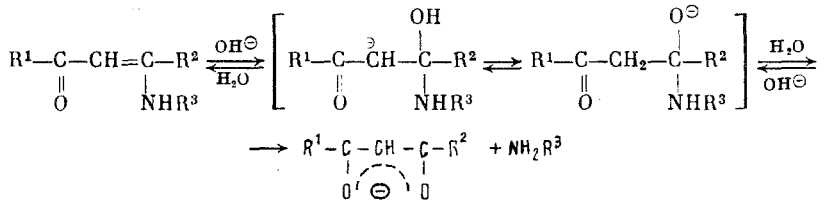
Fig. 3. Relation of rate constants of hydrolysis of (I) (1) and (VI) (2) to pH.

manifested both for the O- and for the C-protonated forms. There is a strong relation of k to the substitution in the ketone part of the molecule. Thus, during substitution of the CF_3 group by the HCF_2CF_2 group, the constant decreased by an order. During C protonation, this part of the molecule would be isolated from the reaction center and would not exert such a strong effect. Apparently, in the limiting step, the water molecule undergoes addition to the O-protonated form of the β-aminovinyl ketone, in which the possibility of delocalization of the positive charge with respect to the chain, including a fluorinated substituent of a phenyl ring, is higher than in the case of the C-protonated form. Abstraction of the amine molecule can occur in various ways, but at this stage the investigations can presuppose the following scheme of the hydrolysis of the β-aminovinyl ketone in the acid medium:



The resulting β-diketones rapidly give adducts with water. This follows from the absence of absorption bands of β-diketones in the analyzed spectral region at acid and neutral pH values.

In an alkaline medium, the β-aminovinyl ketones are rapidly converted to the corresponding β-diketones, which undergo further cleavage more slowly, as was shown spectrophotometrically (Fig. 2). There was a rapid shift of λ_{max} of the β-aminovinyl ketone to values corresponding to λ_{max} of the absorption bands of the β-diketones, and then the absorbance at λ_{max} of the β-diketones decreased comparatively slowly. For compounds (I) and (VI), the linearity of the relation of log k to the pH (pH > 7) with angular coefficient 0.8 is shown. This suggests that the limiting step is the addition of the OH^- ion to the neutral β-aminovinyl ketone molecule. The rate constants measured for compounds (I) and (VII) at pH 12.7 (Table 1) changed within one order, i.e., the effect of the substituents was significantly less pronounced than in acid hydrolysis, although the nature of the effect was similar. This can be explained by the identical nature of the effect of the substituents on the electron-density distribution in the reacting species, which occurred in a comparison of the neutral and O-protonated molecules. The value of the positive charge on the C atom of the enamine group during attack by the strong nucleophile OH^- under the conditions of alkaline hydrolysis did not play such a significant role as in acid hydrolysis. Thus, we can assume the following scheme of hydrolysis of fluoroalkyl-containing β-aminovinyl ketones in an alkaline medium:



LITERATURE CITED

1. Ya. F. Freimanis, Chemistry of Enamino Ketones, Enamino Imines, and Enamino Thiones [in Russian], Zinatne, Riga (1974).
2. J. V. Greenhill, Chem. Soc. Rev., 6, No. 3, 277 (1977).
3. D. N. Sokolov, Gas Chromatography of Volatile Metal Complexes [in Russian], Nauka, Moscow (1981).
4. D. N. Sokolov, Usp. Khim., 57, No. 10, 1670 (1988).
5. L. N. Bazhenova, Dissertation, Chemical Sciences, Inst. Khim. Ural Otd., Akad. Nauk SSSR, Sverdlovsk (1985).
6. J. Kovalec, Said-El-Bahey, and V. Sterba, Collect. Czech. Chem. Commun., 43, No. 10, 2732 (1978).
7. J. K. Coword and T. C. Bruice, J. Am. Chem. Soc., 91, No. 19, 5329 (1969).
8. J. P. Guthril and F. Jordan, J. Am. Chem. Soc., 94, No. 26, 9132 (1972).
9. J. Kovalek, J. Panchartek, T. Potesil, et al., Collect. Czech. Chem. Commun., 51, No. 3, 677 (1986).
10. S. S. Kiselev, M. K. Polievktov, and V. G. Granik, Khim. Geterotsikl. Soedin., No. 12, 1678 (1979).
11. K. I. Pashkevich, V. I. Filyakova, Yu. N. Sheinker, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2087 (1979).
12. K. I. Pashkevich and A. Ya. Aizikovich, Dokl. Akad. Nauk SSSR, 244, No. 3, 618 (1979).
13. V. I. Saloutin, K. I. Pashkevich, and I. Ya. Postovskii, Zh. Vses. Khim. Ova, 21, No. 2, 238 (1976).
14. A. Lovelace, D. Roach, and U. Postelnek, Aliphatic Fluorine-Containing Compounds [Russian translation], IL, Moscow (1961).
15. N. M. Émanuél' and D. T. Knorre, Course in Chemical Kinetics [in Russian], Vysshaya Shkola, Moscow (1969).