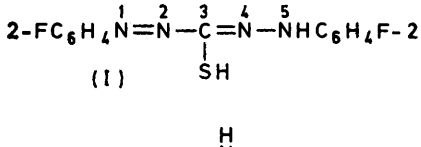
Studies on Dithizone Analogues. Part 3.[1] Kinetics and Mechanism of Cyclodehydrofluorination of 1,5-Bis-(2-fluorophenyl)-3-mercaptoformazan

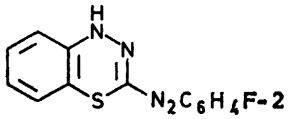
By A. Mageed Kiwan * and Ahmad Y. Kassim, Department of Chemistry, Kuwait University, Kuwait

The dehydrofluorination product of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan (I) in methanol, ethanol, propanol, or glacial acetic acid was isolated and identified as 2-(2-fluorophenylazo)-4*H*-1,3,4,-bnezothiadiazine (II). The stoicheiometry of this reaction was found to be (I) ⟶ (II) + HF. The kinetics have been investigated in various solvents and appropriate mechanisms are suggested.

ALTHOUGH 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan (I) has been recently found [2] to be stable in nonpolar solvents thus allowing its successful application for the determination of metal ions, it decomposes spontaneously in alcohols and acetic acid. Since such behaviour has



(I)



(III)

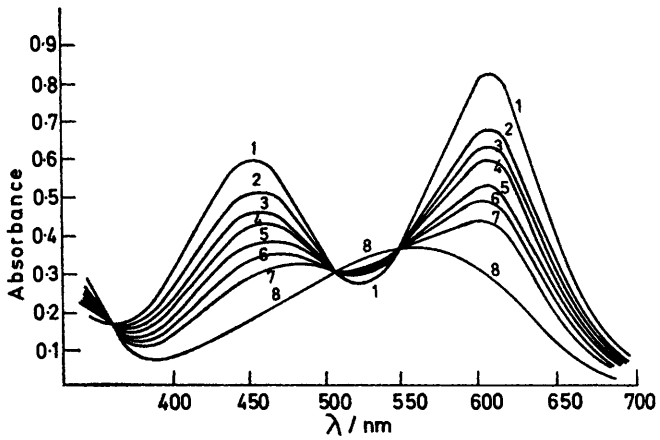
never been reported before with any known dithizone analogues, it was desirable to investigate this novel phenomenon. This paper describes our results on the characterization of the decomposition product and the kinetics of its formation in various solvents.

RESULTS AND DISCUSSION

Identification of the Decomposition Product (II).—The green coloured solution of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan in ethanol was found to change spontaneously to purple and its original absorption maxima at 607 and 450 nm were replaced by a single peak at 548 nm. The presence of isosbestic points in the absorption spectra (Figure) was indicative of the existence of two absorbing species at equilibrium and this was confirmed by the isolation and characterization of the sole decomposition product. Analytical data indicated the loss of one mole of HF per mole of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan, *i.e.*, the decomposition is a dehydrofluorination and its stoicheiometry is (I) ⟶ (II) + HF.

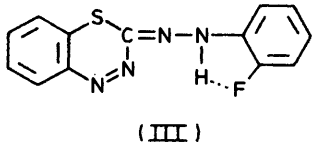
The same dehydrofluorination product has been also obtained by the spontaneous decomposition of (I) in methanol, propanol, or acetic acid. Its i.r. spectra was found to exhibit a strong absorption band at 3 300 cm^{-1} which was assigned to a relatively free NH stretching frequency compared to the corresponding frequency [ν 2 990 cm^{-1} (NH)] of the parent compound. On acetylation this band disappeared and a strong band characteristic of C=O appeared at 1700 cm^{-1}. The presence of the NH group was also confirmed by the ^1H n.m.r. spectra where its signal appeared at τ −1.0 in [$^2H_6$]dimethyl sulphoxide. On shaking with D_2O this signal disappeared and the DOH signal appeared at τ 5.25.

Since the product results from dehydrofluorination of (I), its formation must involve a cyclization reaction

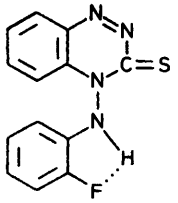


Cyclodehydrofluorination of 3.16 × 10^{-5}M-(I) in ethanol at 51 °C: 1, 0; 2, 6.3; 3, 9.9; 4, 12.6; 5, 18.3; 6, 23.4; 7, 32.7; 8, 54 × 10^2 s

either through sulphur to give (II) or (III), or through nitrogen to give (IV). The spectral (mainly the i.r. and ^1H n.m.r.) characteristics of the dehydrofluorination product are, however, in support of structure (II). This assignment is also in agreement with the recently determined *X*-ray crystal structure of the corresponding bicyclic benzothiadiazine derivative of 1,5-diphenyl-3-mercaptoformazan which is formed by heating it in glacial acetic acid.[3]



(III)



(IV)

We have also prepared the new corresponding bicyclic thiadiazine derivatives of 1,5-bis-(3-fluorophenyl)-, 1,5-bis-(4-fluorophenyl)-, and 1,5-bis-(2-chlorophenyl)-3-

[1] Part 2, A. M. Kiwan and A. Y. Kassim, *Talanta*, 1975, **22**, 931.

[2] A. M. Kiwan and A. Y. Kassim, unpublished results.

[3] W. S. Mcdonald, H. Irving, G. Raper, and D. C. Rupainwar, *Chem. Comm.*, 1969, 292.

mercaptoformazans by heating them in glacial acetic acid. The yields were only *ca.* 40% and their analytical data (see Experimental section) indicated that they were formed by the loss of two atoms of hydrogen per mole of the parent compound, whereas both halogen atoms had remained attached to the phenyl nuclei.

Effect of Solvents on the Cyclodehydrofluorination of (I).—The decomposition of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan in the solvents listed in Table 1 showed a first-order dependence on (I) up to at least 70% complete reaction. An examination of the kinetic data (Table 1) indicated that the rate constants of cyclodehydrofluorination increased in the order of increasing polarity, *viz.*, glacial acetic acid > methanol > ethanol > propanol. The rate of reaction in ethanol was increased further with the addition of HCl up to *ca.* 2.5×10^{-3}M (0.5% v/v HCl in ethanol) beyond which side reactions took place.

The effect of solvents on the electronic absorption spectra of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan was also investigated in the hope of achieving a better understanding of the role played by the solvents. Like 3-mercapto-1,5-diphenylformazan and many other of its known analogues,[4] 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan exhibits two absorption bands at *ca.* 630 and 450 nm,[2] which by analogy, may be attributed to the thione and thiol tautomers respectively. The ratio of their molar absorptivities or what is often described as the peak ratio may also be regarded as a measure of their relative concentration. An examination of the spectral and kinetic data (Table 1) reveals that the rate of cyclodehydrofluorination of (I) is greater in those solvents where it exhibited relatively higher peak ratios, implying that the thione tautomer seems to be the active form involved in the cyclodehydrofluorination.

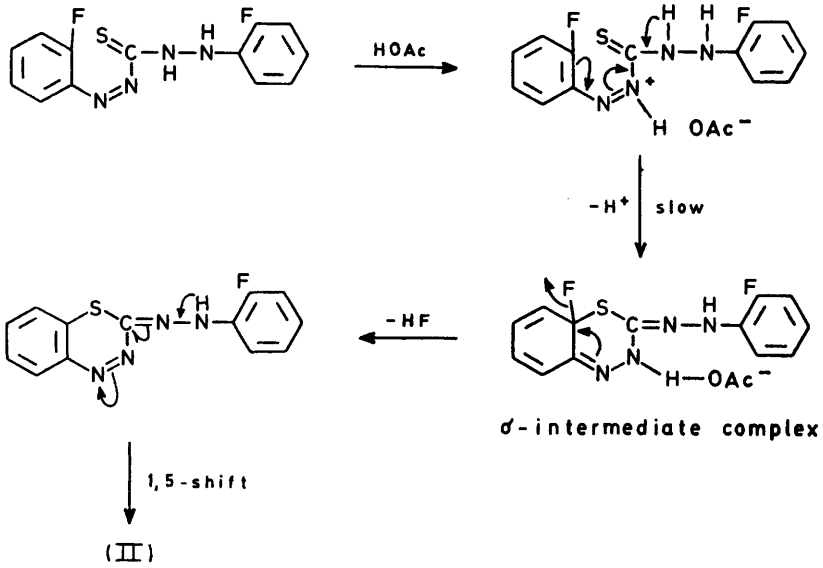
Mechanism of Cyclodehydrofluorination in Ethanol.—Our kinetic results in ethanol and its aqueous solutions may be explained by the following mechanism. The solvation of the thione form (Ia), leads to the development of a partial positive charge at the *o*-carbon atom.

TABLE 1

Rate constants of the cyclodehydrofluorination of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan in various solvents and the corresponding peak ratios

Solvent	Peak ratio	$10^4k/s^{-1}$ 40 °C	45 °C	50 °C	55 °C	60 °C
Methanol	1.55		2.0	3.0		
Ethanol	1.63	1.09	1.7	2.3	3.6	
Propanol	1.41		1.6	2.2	3.4	
Glacial acetic acid	1.70			3.4	4.7	9.5
Ethanol–HCl (2.28×10^{-5}M)	1.65			4.5		
Ethanol–HCl (4.56×10^{-5}M)	1.69			4.66		
Ethanol–HCl (2.28×10^{-4}M)	1.70			5.0		
Ethanol–HCl (2.28×10^{-3}M)	1.75			6.3		
Water–ethanol (5% v/v)	1.17			4.85		
Water–ethanol (10% v/v)	1.07			4.7		
Water–ethanol (25% v/v)	0.85			1.9		
Water–ethanol (35% v/v)	0.64			0.68		
Water–ethanol (15% v/v with 2.28×10^{-4}M-HCl)	1.81			5.1		
Water–acetic acid (5% v/v)	1.70					6.9
Water–acetic acid (10% v/v)	1.70					6.3

This is consequently attacked by the neighbouring sulphur atom to form a σ-intermediate complex (Ic). This complex undergoes a rapid loss of one mole of HF to give (III), which then rearranges through a 1,5-shift to give the cyclodehydrofluorination product (II).



SCHEME 1

Cyclodehydrofluorination in Glacial Acetic Acid.—Protonation as well as solvation of (I) is expected to take

[4] G. Iwantscheff, 'Das Dithizon und Seine Anwendung in der Mikro-und Suprenanalyse,' Verlag Chemie, Weinheim, 1972.

place in acetic acid and cyclodehydrofluorination can be represented by Scheme 2. The addition of water to an acetic acid solution of (I) was found to lower its rate of cyclodehydrofluorination (Table 1) presumably due to decreasing the ability to protonate on dilution.

That the rate of cyclodehydrofluorination was greater

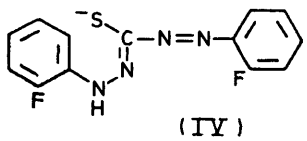
TABLE 2

Activation parameters of the cyclodehydrofluorination of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan in some solvents

Solvent	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$-\Delta S^{\ddagger}$/K cal^{-1} mol^{-1}
Methanol	19.48	18.42
Ethanol	17.30	25.40
Propanol	17.30	25.40
Glacial acetic acid	25.31	0.41

in glacial acetic acid than in the alcohols despite the apparent increase of enthalpy of activation [25.3 *versus* 17.3 kcal mol^{-1} in ethanol (Table 2)] suggests that this reaction is entropy controlled as was indeed confirmed by the relative higher $\Delta S^{\ddagger}$ (−0.43 in glacial acetic acid *versus* 25.40 cal K mol^{-1} in ethanol). This may be attributed to the relatively less restricted geometry of the transition state in acetic acid compared to the more ordered configuration of the corresponding σ-complex (Ic) in ethanol.

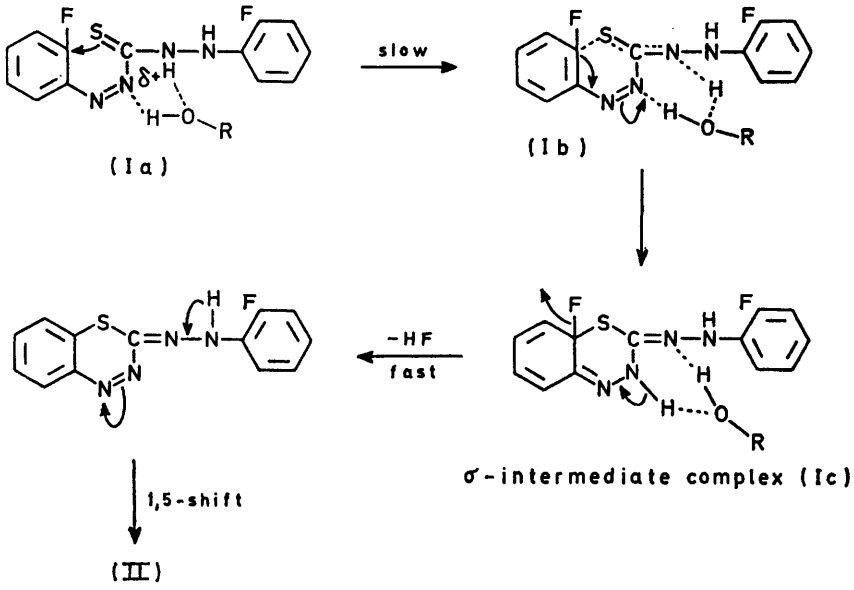
Although water is more polar than ethanol and may be



(IV)

expected to enhance the cyclodehydrofluorination of (I) perhaps due to more effective solvation of the transition state as observed for 5 and 10% water–ethanol mixtures, its higher basicity seems to outweigh its polarity particularly as its concentration increases further (Table 1) and hence increases the ionization of 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan (pK_a 4.05).[2] The resulting negatively charged thiolate ion is presumably twisted to keep the sulphur and fluorine atoms apart [conformation (IV)] and hence prevents cyclodehydrofluorination. This explanation is further supported by the finding that no cyclodehydrofluorination takes place in alkaline medium where 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan exists mainly as the thiolate anion.[2]

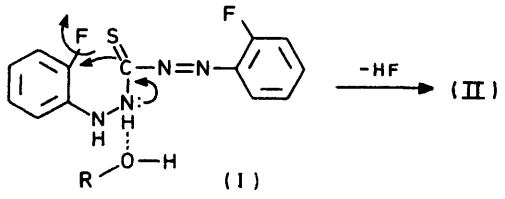
The cyclodehydrofluorination of (I) in ethanol by 3,6-dehydrofluorination need not be excluded (Scheme 3). It involves the solvation of the imino proton attached to N(4) followed by the nucleophilic attack of sulphur on the *o*-carbon atom which results in the liberation of one mole of hydrofluoric acid and the formation of the cyclodehydrofluorination product, (II). However, since the cyclodehydrofluorination of (I) in glacial acetic acid probably involves the protonation of the azo-group of



SCHEME 2

(I) rather than the imino-group, 3,6-dehydrofluorination seems rather unlikely.

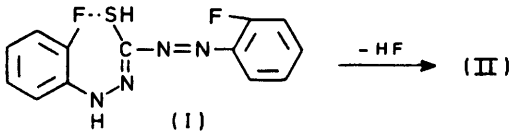
Cyclodehydrofluorination involving the thiol form of (I) (Scheme 4) may be ruled out because (i) the reaction



SCHEME 3

does not proceed in aprotic solvents such as chloroform or carbon tetrachloride and (ii) 1,5-bis-(2-fluorophenyl)-3-mercaptoformazan is an acid with a pK of 4.05 [2] which suggests the presence of an appreciable concentration of thiolate anion (as a result of ionization) the ex-

pected configuration (IV) of which would prevent cyclization.



SCHEME 4

EXPERIMENTAL

1,5-Bis-(2-fluorophenyl)-3-mercaptoformazan (I).—This was prepared by Bamberger's nitroformazyl method [5] and the details will be published elsewhere.

2-(2-Fluorophenylazo)-4H-1,3,4-benzothiadiazine (II).—This was prepared by heating formazan (I) (0.5 g) in freshly distilled ethanol (100 ml) at 60 °C for *ca.* 1.5 h. The solvent was then evaporated and the solid product was purified by crystallization from ethanol–water as reddish bronze *needles* (93%) (Found: C, 57.3; H, 3.3; N, 21.5; F, 7.0; S, 12.3. $C_{13}H_9FN_4S$ requires C, 57.3; H, 3.2; N, 20.1; F, F, 6.95; S, 11.3%), m.p. 200°, mol. wt 270 (osmometric in ethanol), $\lambda_{max.}$ (EtOH) 548 nm (ε 10 300).

The same product was also obtained by heating under reflux (I) (1 g) in glacial acetic acid (50 ml) for *ca.* 1 h. The mixture was cooled in ice, neutralized with sodium hydroxide, and extracted with benzene. Removal of the solvent left the crude product which was purified chromatographically on alumina using 1% methanol in benzene as eluant.

Other Analogues of (II).—The corresponding derivatives of 1,5-bis-(3-fluorophenyl)-, 1,5-bis-(4-fluorophenyl)-, and 1,5-bis-(2-chlorophenyl)-3-mercaptoformazans were prepared by heating the formazans in glacial acetic acid and finally purified as mentioned above. Their elemental analyses and m.p.s are given in Table 3.

Determination of Liberated Hydrofluoric Acid.—Compound (I) in (0.50 g) freshly distilled ethanol (100 ml) was heated at 60 °C for *ca.* 1.5 h. The mixture was then cooled and poured over water (100 ml) and the precipitate was extracted by shaking with several aliquot portions (25 ml) of chloroform until the aqueous phase became colourless. The volume of the aqueous phase was made up to 500 ml with deionized water. The concentration of hydrofluoric acid was determined in a known volume by titration with a standard sodium hydroxide solution. The concentration of fluoride ions were determined in another volume by titration with standardized thorium nitrate in the presence of sodium alizarin sulphonate as indicator.[6]

Kinetics.—Cyclodehydrofluorination of (I) was followed spectrophotometrically as follows. If A_1 and A_2 are the absorbances at 607 nm [the wavelength of maximum absorption of (I)] and at 548 nm [the wavelength of maximum absorption of (II)] ε_1 and ε'_1 are the molar absorptivities of (I) at 607 and 548 nm respectively, and ε_p and ε'_p are the molar absorptivities of (II) at 607 and 548 nm respectively, the concentration of (I) is calculated by equation (1).

$$[(I)] = \varepsilon_p A_2 - \varepsilon'_p A_1/\varepsilon_1\varepsilon_p - \varepsilon_1\varepsilon_p' \qquad (1)$$

Spectroscopic Measurements.—U.v.–visible spectra were recorded on a Unicam SP 8000 recording spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Varian A60 (60 MHz) spectrometer. The i.r. spectra were recorded on a Beckmann IR 12 spectrophotometer.

Elemental Analyses.—These were done at Alfred Bernhard Mikroanalytisches laboratorium, West Germany.

TABLE 3

Physical and analytical data for 4*H*-1,3,4-benzothiadiazine derivatives

Derivative		C (%)	H (%)	N (%)	S (%)	Halogen (%)	M.p. (°C)
3-Fluorophenyl-azo-6-fluoro	Found	53.6	2.8	19.2	11.0	13.2	201
	Reqd.	53.35	2.85	19.3	11.05	13.1	
4-Fluorophenyl-azo-7-fluoro	Found	53.4	2.9	18.6	10.7	12.5	165
	Reqd.	53.35	2.85	19.3	11.05	13.1	
2-Chlorophenyl-azo-5-chloro	Found	49.0	2.7	16.7	9.7	20.9	234
	Reqd.	48.3	2.45	17.35	9.9	22.0	

[6/1046 *Received*, 2*nd June*, 1976]

[5] D. M. Hubbard and E. W. Scott, *J. Amer. Chem. Soc.*, 1943, **65**, 2390.

[6] W. D. Armstrong, *Ind. and Eng. Chem.* (*Analyt. Edn.*), 1936, **8**, 384.