Kinetic Studies of Nucleophilic Substitution of Various Halothiadiazoles with Methoxide Ion

B. Modarai, M. H. Chandehari and H. Massoumi

Department of Chemistry, Arya-Mehr University of Technology
Tehran, Iran

and

A. Shafiee, I. Lalezari and A. Badali

Department of Chemistry, Faculty of Pharmacy,
University of Tehran, Tehran, Iran

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A number of halo-substituted 1,2,3 and 1,3,4-thiadiozoles have been prepared, their reactivity towards methoxide ion have been studied and the kinetic parameters are reported.

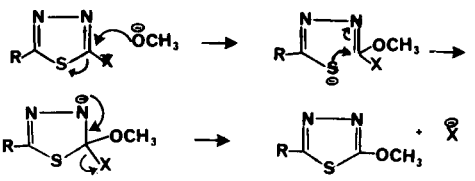
It has been shown that halofurans, although slightly more reactive than their benzene analogues, would only undergo nucleophilic substitution at elevated temperatures (1). Except for the 2-halogen derivatives, thiazoles are reported to be generally inert towards displacement reactions under ordinary conditions (2). Kinetic data are available for the substitution of 2-chlorothiazole and 2-chlorobenzothiazole with piperidine (3).

To date no kinetic investigation has been carried out on substitution reactions of 1,3,4- and 1,2,3-halothiadiazoles. It has, however, been reported that 3-halogeno-1,2,4-thiadiazoles are quite inert towards most nucleophilic reagents (4), and that the 5 position is more reactive and the reaction of the 5-halogeno-1,2,4-thiadiazole with different nucleophiles has been reported (5). The present work investigates the kinetics and the most likely mechanism of substitution reactions of chloro and bromo derivatives of 1,2,3- and 1,3,4-thiadiazoles with sodium methoxide in methanol. These compounds show enhanced reactivity towards nucleophilic substitution.

The kinetic results, shown in Table I, indicate that the 1,3,4-derivatives are generally more reactive than the 1,2,3-compounds. The presence of a phenyl group causes an increase in reactivity. Table I also indicates that the chloro compounds are slightly more reactive than the bromo analogues. From this it may be inferred that the breakage of the C-X bonds are not important in the activation process for these substitutions.

In order to determine the possibility of a ring opening mechanism experiments were performed once in the presence of three moles of methyl iodide (for every mole of halothiadiazole) and then in the presence of three moles of methyl vinyl ketone (for every mole of halothiadiazole) and no $R\text{-}C(SCH_3)=N\text{-}N=C(X)\text{-}OCH_3$ or $R\text{-}C(SCH_2CH_2\text{-}C(=O)\text{-}CH_3)=N\text{-}N=C(X)\text{-}OCH_3$ were obtained for the two experiments respectively. The experiment was also performed in presence of one mole of $CH_3O\text{-}C(=O)\text{-}OCH_3$ and no $CH_3O\text{-}C(=O)\text{-}S\text{-}C(R)=N\text{-}N=C(X)\text{-}OCH_3$ was obtained. The results indicate that the idea of a ring opening mechanism by scheme I is extremely speculative.

Scheme I



A feasable mechanism consistent with the results is presented in Scheme II for 2-halogeno-1,3,4-thiadiazole.

Scheme II

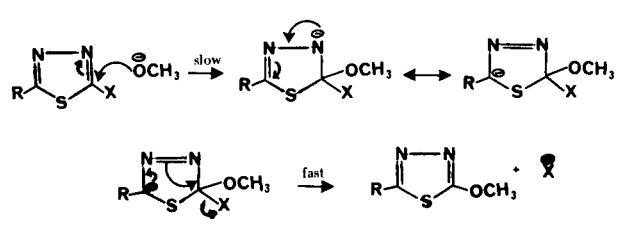


TABLE I

Kinetic Parameters of Halogen Displacement Reaction in 1,2,3- and 1,3,4-Thiadiazoles.

Compounds	T, °C	k(lit mole^{-1} sec^{-1})	ΔE# (Kcal)	ΔG# (Kcal) (a)	ΔS# (e.u.) (a)
5-Chloro-4-mehtyl-1,2,3-thiadiazole	34.0	6.9×10^{-6}	22.5	25.3	-10.7
	44.0	2.2×10^{-5}			
	54.0	6.3×10^{-5}			
5-Chloro-4-phenyl-1,2,3-thiadiazole	34.0	1.6×10^{-4}	20.0	23.5	-12.9
	44.0	5.0×10^{-4}			
	54.0	1.3×10^{-3}			
2-Chloro-5-methyl-1,3,4-thiadiazole	34.5	1.3×10^{-3}	17.5	22.4	-17.0
	44.0	3.0×10^{-3}			
	54.0	6.4×10^{-3}			
2-Bromo-5-methyl-1,3,4-thiadiazole	34.0	6.0×10^{-4}	18.1	22.8	-16.3
	44.0	1.8×10^{-3}			
	54.0	3.7×10^{-3}			
2-Chloro-5-phenyl-1,3,4-thiadiazole	34.0	7.0×10^{-3}	12.5	21.8	-30.0
	44.0	1.3×10^{-2}			
	54.0	2.4×10^{-2}			
2-Bromo-5-phenyl-1,3,4-thiazole	34.0	3.9×10^{-3}	13.2	21.9	-28.8
	44.0	8.0×10^{-3}			
	54.0	1.4×10^{-2}			

(a) Calculated from rate constants at 54°.

In line with the mechanism we have presented, it may be inferred that the stronger electron attracting power of the chlorine atom than bromine lowers the electron density at the center of reaction so that attack by the base becomes more favorable energetically. It may also be said that the massive bromine atom causing a greater steric hindrance gives rise to a slower reaction rate.

The above mechanism also accounts for the very rapid reaction rate of 2-halo-5-trifluoromethyl-1,3,4-thiadiazole. The powerful electron withdrawing ability of the trifluoromethyl group causes such enhanced reactivity that rate measurements could not be performed even at -30°.

Attempts to obtain kinetic results for 2-halo-5-methyl-1,3,4-selenodiazoles failed since the compounds decomposed under the experimental conditions used. Also kinetic studies could not be performed on 2-bromo-5-meta-nitrophenyl-1,3,4-thiadiazole since the compound was insoluble in methanol.

EXPERIMENTAL

Preparations.

The 2-halo derivatives of 5-R-substituted 1,3,4-thiadiazoles were prepared by the diazotization of the corresponding amino compounds according to the method of Kanaoka (6).

2-Chloro-5-methyl-1,3,4-thiadiazole.

This compound had m.p. 69-70° (lit. (6) 70-71°).

2-Bromo-5-methyl-1,3,4-thiadiazole.

This compound had m.p. 107° (lit. (7) 107.5-108°).

2-Chloro-5-phenyl-1,3,4-thiadiazole.

This compound had m.p. 88° (lit. (8) 88°).

2-Bromo-5-phenyl-1,3,4-thiadiazole.

This compound had m.p. 90° (lit. (9) 84-85°).

2-Bromo-5-meta-nitrophenyl-1,3,4-thiadiazole.

This compound had m.p. 196°.

Anal. Calcd. for $C_8H_4BrN_3O_2S$: C, 33.56; H, 1.39; N, 14.68. Found: C, 33.68; H, 1.38; N, 14.59.

2-Bromo-5-methyl-1,3,4-selenadiazole.

This compound had m.p. 105°; m/e 227.

Anal. Calcd. for $C_3H_3BrN_2Se$: C, 15.85; H, 1.32; N, 12.33. Found: C, 15.74; H, 1.41; N, 12.51.

2-Bromo-5-trifluoromethyl-1,3,4-triadiazole.

This compound had b.p. 74-76°/20 mm.

Anal. Calcd. for $C_3BrF_3N_2S$: C, 15.45; N, 12.01; S, 13.73. Found: C, 15.38; N, 11.98; S, 13.81.

2-Chloro-5-trifluoromethyl-1,3,4-thiadiazole.

This compound had b.p. 153-154°.

Anal. Calcd. for $C_3ClF_3N_2S$: C, 19.09; N, 14.85; S, 16.97. Found: C, 19.12; N, 14.78; S, 16.84.

The 5-chloroderivatives of 4-R-substituted-1,2,3- thiadiazoles required for this work were prepared according to the modified method of Hurd and Mori (10).

5-Chloro-4-methyl-1,2,3-thiadiazole.

Thionyl chloride (15 ml.) was added at 0° to 5.47 g. (0.03 mole) of α-chloroacetone semicarbazone. When the evolution of gas ceased, the mixture was added to a cold saturated solution of sodium bicarbonate and extracted with chloroform. The chloroform layer was separated and washed with water, dried over sodium sulfate and evaporated. The residue was distilled and the fraction boiling at 182-183° was collected (3.40 g., 80%).

Anal. Calcd. for $C_3H_3ClN_2S$: C, 26.76; H, 2.23; N, 20.81;

Cl, 26.39. Found: C, 26.68; H, 2.15; N, 20.92; Cl, 26.42.

5-Chloro-4-phenyl-1,2,3-thiadiazole.

This compound was prepared similarly and the product was steam distilled and crystallized from ether-petroleum ether, m.p. 100°.

Anal. Calcd. for $C_8H_5ClN_2S$: C, 48.24; H, 2.54; N, 14.24; Cl, 18.06. Found: C, 48.31; H, 2.56; N, 14.36; Cl, 18.01.

Kinetic Measurements.

Pseudo-first order rate constants were obtained as follows: solutions of the halide at concentrations of about 0.1 to 0.2 g./50 ml. were prepared by dissolving the compound in methanol. To 3 ml. aliquots kept at constant temperature, 3 ml. of 0.1 to 1 *M* sodium methoxide kept at the same temperature as that of the halide was added. The reaction vessel was covered to prevent evaporation and to prevent atmospheric carbondioxide from reacting with the solution. The reaction was quenched with 5 ml. of 2 *N* nitric acid at recorded times, and the resulting solution was titrated with 0.025 *N* silver nitrate using silver-Calomel electrodes. The tritration cell consisted of three compartments connected by G.4 glass filters. Ammonium nitrate (0.1 *M*) was placed in the middle compartment to act as a conducting electrolyte. A *p*H meter Model 292 made by Pye Unicam was used. Activation energies were calculated from rate constants at 34°, 44° and 54°.

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