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Studies on Dithiocarbamates. XII. Kinetic Studies on the Hydrolysis of Mesoionic 4,5-Diphenyl-1,3,4-thiadiazole

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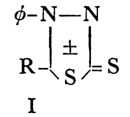
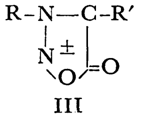
Kinetic studies of the compound given in the title were conducted in aqueous alcohols over a wide range of pH. The observed rate constants are dependent on the hydroxide-ion concentration as well as polarity of the medium. Hydrolytic decomposition is characterised by a small magnitude of entropy (ΔS^*) and negative salt-effect. Mechanism consistent with these facts has been suggested.

We had been interested for some time in the physicochemical properties of heterocyclic systems containing -NCS fragment as an essential part of their structure.[1–4] In continuation of this work, we recently reported[5] the synthesis and spectral characteristics of a series of mesoionic 1,3,4-thiadiazoles (I). This provided us with an opportunity to examine the hydrolytic behaviour of a typical compound (II) as a representative member of the series.



I
II, R=ϕ



III

Quite apart from their structural peculiarities,[6,7] mesoionic compounds (I and III) were also reported to have interesting pharmacological properties.[6,7] Consequently, fairly extensive kinetic[8–10] data are now available on more readily accessible sydnone derivatives (III), which show sensitivity to both acid and alkali. Comparative data on mesoionic thiadiazoles (I) are highly desirable as it is anticipated that any intrinsic difference in properties between these two systems is bound to have profound reflection on the observed data. With this objective in view, our studies are mainly concerned with effects of pH, temperature, solvent composition and ionic strength on the rate constants. These results, in conjunction with the isolation of a derivative of the product of hydrolysis in alkaline condition provide sufficient evidence on the probable course of degradation of II under alkaline condition.

Experimental

Materials. Mesoionic 4,5-diphenyl-1,3,4-thiadiazole (II) has been previously described.[5,7] AR-grade solvents were fractionated over metallic sodium and mid-fractions were stored in amber-coloured bottles

TABLE 1. THE APPARENT FIRST ORDER RATE CONSTANTS UNDER VARIOUS EXPERIMENTAL CONDITIONS AT 25°C

No.	Solv. comp. % solv. (v/v)	Experimental pH	Ionic str. μ	Rate const $10^4\times k_{ob}$ in sec^{-1}	Calcd second order rate const. k in l/mol/sec
1	50-EtOH	7.80	0.05	0.006489	1.028
2	50-EtOH	8.30	0.05	0.02079	1.042
3	50-EtOH	8.70	0.05	0.09137	1.854
4	50-EtOH	9.60	0.05	0.561	1.409
5	50-EtOH	10.10	0.05	1.381	1.097
6	50-EtOH	10.50	0.05	4.606	1.456
7	50-EtOH	10.70	0.05	7.170	1.431
8	50-MeOH	9.55	0.05	1.421	4.005
9	50-*i*-PrOH	10.55	0.05	4.103	1.156
10	50-EtOH	10.55	0.25	3.070	0.865
11	50-EtOH	10.55	0.50	2.457	0.692
12	40-EtOH	10.30	0.05	3.141	1.574
13	30-EtOH	10.10	0.05	2.214	1.759
14	30-EtOH	10.10	0.25	1.706	1.355
15	30-EtOH	10.10	0.50	0.959	0.762

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1) P. B. Talukdar, *J. Indian Chem. Soc.*, **44**, 17 (1967).

2) P. B. Talukdar and S. Banerjee, *ibid.*, **44**, 1060 (1967).

3) P. B. Talukdar and S. K. Sen Gupta, *ibid.*, **45**, 291 (1968).

4) P. B. Talukdar, S. Banerjee and A. Chakraborty, *ibid.*, **45**, 775 (1968).

5) P. B. Talukdar and S. K. Sen Gupta, *ibid.*, in press; *ibid.*, **45**, 356 (1968), for short communication.

6) L. B. Kier and E. B. Roche, *J. Pharm. Sci.*, **56**, 149 (1967).

7) T. G. Stewart and L. B. Kier, *ibid.*, **54**, 731 (1965).

8) E. R. Garrett, *ibid.*, **53**, 42 (1964).

9) E. R. Garrett and P. J. Mehta, *ibid.*, **56**, 1468 (1967).

10) S. A. Zotova and V. G. Yashunskii, *Zh. Org. Khim.*, **3**, 942 (1967).

prior to their uses, and calibrated by checking their specific-gravities against literature values. Conductivity water was prepared in an all-glass apparatus from distilled water over potassium permanganate.

Acetate buffers were used for studies under acidic conditions, but phosphate and borate buffers were used under alkaline conditions; ionic strength (μ) was maintained at around 0.1 with requisite amount of KCl and the pH values were checked in a standard Cambridge pH-meter. The pH values recorded in Table 1 refer to those observed under the actual experimental condition (after 24 hr) after mixing the required amount of solvents and stock buffers. Higher ionic strength was achieved through addition of extra amount of KCl to the required quantity of buffer.

Spectrophotometric measurements were carried out with a Hilger UVISPEK spectrophotometer in 1 cm cells.

Kinetic Measurements. Initial experiments have shown that the characteristic long wavelength band[5,7] of the mesoionic thiadiazole appears at 382—383 mμ under the projected experimental condition, and the band position remains practically unchanged with change in pH; hence all kinetic runs were followed by measuring the loss of intensity of this band at 382 mμ.

A fairly concentrated solution of the substrate was first prepared in an appropriate solvent so that the observed optical density is around unity. After the thermal equilibration of the stock solutions, aliquots were mixed and the fall in intensity was followed until at least 80% of the substrate reacted. Other details were the same as before.[2,4]

Constancy of the thermostatic bath was within ± 0.2°C and the accuracy of the data was better than 3% by agreement between duplicate experiments.

Product Study. 200 mg of the compound was first dissolved by warming in about 30 m*l* of ethanol; it was cooled to 25°C and diluted with an equal volume of water. To the yellow solution, aqueous NaOH (10%) was added dropwise with stirring at 25°C maintaining the pH at 9—10. When there was no more fading away of colour (about 30 min), pH was adjusted at 5—6 with drops of acetic acid and gently warmed on a steam bath for about 5 min. A solution of *p*-nitrobenzaldehyde (120 mg) in minimum quantity of alcohol was added with swirling to the above solution and the mixture was heated on a steam bath for another 10 min. On cooling down to room temperature, a yellow precipitate was obtained; this was collected, washed with a few drops of ethanol.

Two crystallisations from ethanol yielded 85 mg (50%) of pale yellow needles, mp 149.5—150°C, with immediate solidification and remelts at 169—170°C; λ_{max}^{EtOH} 226 mμ (ε, 18750) and 325 mμ (ε, 20060). IR (Nujol): 1660 (-CO, amide) and 1640 (-C=N) cm^{-1}. Found: N, 12.28%. Calcd for $C_{20}H_{15}N_3O_3$: C, 12.17%.

Identity of the product was established by comparison with an authentic sample of *p*-nitrobenzylidene derivative (IX) of *N*-benzoyl-*N*-phenylhydrazine synthesized by the following method:

A solution of phenylhydrazone of *p*-nitrobenzaldehyde (200 mg; mp 159—160°C) in 30 m*l* of dry benzene was refluxed with equimolar amounts of benzoyl chloride and pyridine for 10 hr. After working up in the usual way, the residue was crystallised from ethanol to give pale yellow needles, mp 169—170°C, with similar characteristics and identical absorption bands as the above compound.

Results and Discussion

Effects of pH and Temperature. The apparent first order rate-constants at various pH in 50% aqueous ethanol are shown in Table 1. Data clearly show appreciable acceleration of rate with rise in pH so much so that it is extremely difficult to measure the rate at a higher pH (>10.5). On the other hand, the reaction is extremely sluggish between pH 7—8 and there was practically no change in optical density in acidic buffers (4.90 and 3.65) over a week.

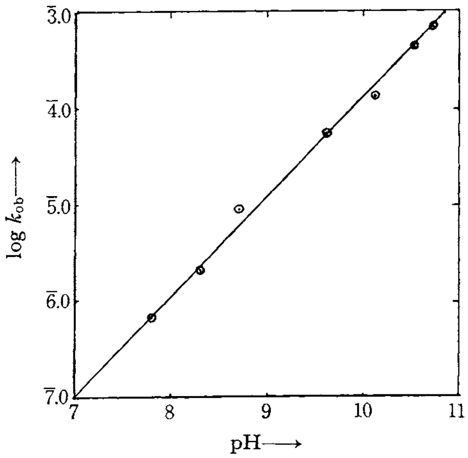

Fig. 1. pH-rate profile in 50% aqueous ethanol at 25°C and μ=0.05.

The observed behaviour of II in the acidic region is quite a surprise when one recalls the facile degradation of sydnones under a similar condition to yield the appropriate hydrazines.[10,11] However, the significance of the data becomes readily comprehensible from the pH-rate profile (Fig. 1) where the slope is almost equal to unity suggesting specific hydroxide-ion catalysed reaction at the rate-limiting step. Presumably, the reaction is first-order with respect to hydroxide ion concentration. Similar specific hydroxide-ion catalysed hydrolysis has been observed with some sydnone derivatives.[9]

That the observed reaction is also first-order with respect to the substrate is shown not only by the excellent first-order plots (log o.d. *vs.* time), but also by the constancy of half-lives ($t_{1/2}$=24—25 min) at five different initial concentrations (0.8 to 2.0×10^{-3}M) of the substrate in 50% ethanol at 25°C for pH=10.5 and μ=0.05. Evidently, the overall reaction is a clean second-order one. Hence, the rate law for the observed reaction is

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[11] R. A. Eade and J. C. Earl, *J. Chem. Soc.*, **1946**, 591.

$$-\frac{\mathrm{d}A}{\mathrm{d}t} = k[\mathrm{A}][\mathrm{OH}]^-$$

$$= k_{\mathrm{ob}}[\mathrm{A}], \text{ for a given pH.}$$

Thus $k_{\mathrm{ob}}=k[\mathrm{OH}]^-$, hence the bimolecular rate-constants for the hydroxide-ion catalysed reaction could be obtained from k_{ob}; these are shown in Table 1 and are reasonably constant under identical conditions (No. 1—7).

TABLE 2. TEMPERATURE DEPENDENCY OF RATE CONSTANTS IN 50% AQUEOUS ETHANOL AT pH=10.50 AND μ=0.05

Temp. °C	$10^4\ k_{\mathrm{ob}}$ in sec^{-1}	Kinetic parameters
15	1.379	E_{A}=20.19 kcal/mol
20	2.239	ΔH^*=19.60 kcal/mol
25	4.606	ΔG^*=22.02 kcal/mol (at 25°)
30	7.932	ΔS^*=−8.13 e.u.

Data on the temperature dependency of rate-constants are shown in Table 2. The derived activation parameters are quite comparable to those reported[9] for the base-catalysed decomposition of sydnones and to other bimolecular reactions. Although the absolute value of ΔS^* could not be emphasized, the small negative value is highly significant. It is now recognised that, for a unimolecular reaction, the magnitude of ΔS^* is usually very small and tends to be zero.[12] Interpretation of such data is extremely difficult,[13] but in the given instance it undoubtedly reflects the small difference between the reactant and the transition-state with respect to their imposed constraints. The situation could be resolved by assuming the formation of an initial transition complex through the rate-determining attack of the hydroxide ion followed by smooth and rapid rearrangement to another intermediate prior to its decomposition.

The Effect of Variation in Solvent Composition. The influence of the variation in solvent composition on the rate-constant is also included in Table 1. Although the same quantity of buffer was used in each case, and the ionic strength was maintained at the same level, the observed pH of the medium, as anticipated, shows considerable variation with change in the nature of the co-solvent. The impact of solvent composition on the rate-constants is, therefore, apparently submerged in the apparent first-order rate-constants due to inherent difference in pH of the medium. Assuming that there is no significant difference in the ionisation of water for the solvents under consideration, the calculated second-order rate-constants clearly demonstrate the expected order of solvent effect where the rate-constants increase with increasing polarity of the medium. This apparently indicates ionic character of the transition state. But no attempt is made here to correlate the rate-constants with any known[14] parameter of the solvent, because microscopic polarity in the cybotactic[15] region of the reacting species is extremely difficult to be adequately expressed by known parameters of the solvent.

Parker[16] has already discussed the mode of solvation in a protic solvent where hydrogen-bonding is considered to play a vital role. It has already been observed by us[5] that λ_{max} of the thiadiazole (II) is quite sensitive to the protic character of the solvent. In the given instance, then, it might be true that the increased population of a specific dipolar form[6,7] of II (which is stabilised through hydrogen-bonding) makes an effective contribution in increasing the rate in a more polar solvent. At the same time, solvation to the transition-state, which is largely anionic in character, appears to be favoured in more polar medium suggesting appreciable charge dispersion[17] at the transition state. This ought to be viewed against the small magnitude of ΔS^* as noted earlier. Although no attempt has been made to find out the changes in ΔS^* by changing the solvent composition, it is probably the difference in the solvation of the reactant[18] rather than the transition-state that appears to be important here; however, possibility of the changes in ΔH^* can not be altogether discarded and the origin of the solvation effect is still a matter of debate.[19]

From all accounts, it appears reasonable to exclude water as a direct participant and its role is essentially associated with solvation phenomenon. Thus, kinetic data in solvents of similar composition (50% aqueous methanol, ethanol and 2-propanol, Table 1) tend to confirm this, but comparatively higher rate in 50% methanol may be due to some other specific interactions. Alternatively, hydroxide-

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12) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

13) C. A. Bunton and V. J. Schiner, *J. Amer. Chem. Soc.*, **83**, 3207 (1961).

14) C. C. Reichardt, *Angew. Chem. Int. Ed. Engl.*, **4**, 29 (1965).

15) E. M. Kosowar, "An Introduction to Physical Organic Chemistry," John Wiley & Sons, New York (1968), p. 262.

16) A. J. Parker, *Advan. Phys. Org. Chem.*, **5**, 173 (1967).

17) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, New York (1963), p. 267.

18) Y. C. Mac, W. A. Millen, A. J. Parker and W. D. Watts, *J. Chem. Soc., B*, **1967**, 525; R. Alexander, K. C. F. Ko, A. J. Parker and T. J. Broxton, *J. Amer. Chem. Soc.*, **90**, 5049 (1968).

19) J. E. Crooks, *Annual Reports, The Chemical Society* (London), **64**, 37 (1967).

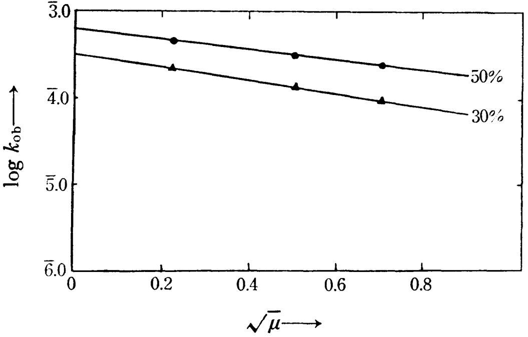


Fig. 2. Effect of electrolyte on the rate.

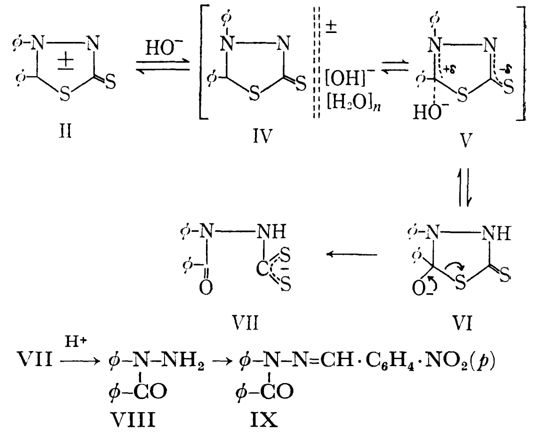
ion is known to be a structure-maker[20] and with a suitable orientation may lower the activation energy in the formation of the tetrahedral intermediate (see below).

Salt-effect on the Rate Constants. Data for the effect of the ionic strength (μ) in the reaction medium are presented in Table 1 for three different alcohol-water compositions. In all cases rate retardation is observed for increased values of μ. Qualitatively, this is consistent with the salt-effect upon ion-molecule reaction;[21] for example, fairly large electrolyte effect is observed for the attack of hydroxide-ion on *p*-nitrodiphenylphosphate in water.[22] Actually, the plots of log k_{ob} against $\sqrt{\mu}$ is linear (Fig. 2), the lower the proportion of alcohol, the larger the slope (-0.6 and -0.75 at 50% and 30% ethanol respectively). Again, from the plot of the slope against % water, the intercept yields a value almost equal to unity. Thus the predicted salt-effect in absence of alcohol (*i. e.*, in 100% water) has got the value as required by limiting Deybe-Hückel equation for reaction between two oppositely charged species, each carrying a unit charge.

However, our results could not be directly compared with those reported[9] for sydnones where the effect of electrolyte on the acid-catalysed reaction was examined. But it is still more difficult to account for such salt-effects as pointed out recently by Bunton and Robinson.[29] According to them it is highly unlikely that ion-pairing is important in aqueous alcohol. Further, possibility of changing the lyate ion from OH^- to more nucleophilic alkoxide-ion[23] with increase in alcohol content could not be a significant factor under the experimental set up. It has also been suggested[20] that for anion-molecule reaction in polar hydroxylic solvent, the transition state is stabilised relative to the nucleophilic anion by cations of low charge density (*e. g.* K^+) and this is apparently consistent with our observation.

Alternatively, the negative salt-effect may be attributed to preferential solvation of K^+ and Cl^- by water so that less water is available as solvating species.[24] The magnitude of salt-effect should, in that case, be more pronounced in a less polar medium; but this is contrary to our experience. Consequently, the observed electrolyte effect could be reasonably attributed to its interaction at the transition-state.

Product Isolation and Mechanism of Degradation. Any mechanistic interpretation on the alkaline decomposition of II must, therefore, satisfy the following facts: (1) first-order dependence on hydroxide-ion concentration, (2) rate increases with increased polarity of the medium, (3) small magnitude of ΔS^*, and (4) the negative salt-effect. In accordance with these facts the following scheme is suggested:



$$\mathrm{VII} \xrightarrow{H^+} \underset{\underset{\text{VIII}}{\phi\text{–CO}}}{\phi\text{–}\underset{|}{N}\text{–}NH_2} \rightarrow \underset{\underset{\text{IX}}{\phi\text{–CO}}}{\phi\text{–}\underset{|}{N}\text{–}N{=}CH\cdot C_6H_4\cdot NO_2(p)}$$

The most difficult step in the proposed scheme is to locate the site of the attack of hydroxide-ion. The same difficulty was encountered in explaining the base-catalysed decomposition of sydnones and consequently, two alternative mechanisms, involving positions 2 and 5 were proposed.[8,25] It is difficult to comprehend a situation where the attack of hydroxide-ion occurs on the carbon atom bearing the exocyclic sulphur atom with a large formal negative charge. In this respect we are in agreement with the views of Garrett[8] on sydnone derivatives.

What is intended here is to show that the solvated thiadiazole (II) becomes highly polarised by the approach of the hydrated hydroxide-ion so as to form a complex (IV) in a rate determining step.

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[20] C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 5965 (1968).

[21] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York (1953), Chap. VII.

[22] C. A. Bunton, S. Farber and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).

[23] R. G. Burns and B. D. England, *Tetrahedron Lett.*, **1960**, 1.

[24] N. B. Chapman, E. Ehsan, J. Shorter and K. J. Toyane, *J. Chem. Soc., B*, **1968**, 178.

[25] E. B. Roche and L. B. Kier, *Tetrahedron*, **24**, 1672 (1968).

This rapidly rearranges, possibly involving OH$^-$ transfer through water clusters,[26] to give the tetrahedral intermediate (VI). The intermediate, in turn, collapses in a fast step to yield the dithiocarbazinate (VII) under the alkaline condition. In support of the main sequence of the reaction, we have already isolated *N*-benzoyl-*N*-phenylhydrazine (VIII) as *p*-nitrobenzylidene derivative (IX) in fair yield. Isolation of the same compound in a poorer yield has been recently claimed[27] but no data were provided. We plan to continue our studies in order to resolve the details of the proposed mechanism.

We thank Mr. P. Bagchi, Research Director, for his keen interest and Dr. S. K. Das Gupta for IR spectra.

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26) Ref. 15, p. 287.

27) R. Grashey, M. Bauman and W. D. Lubos, *Tetrahedron Lett.*, **1968**, 5881.