Tetrahedron, 1965, Vol. 21, pp. 843 to 848. Pergamon Press Ltd. Printed in Northern Ireland

A QUANTITATIVE STUDY OF THE UNCATALYSED HALOGENATION OF THIOPHENE IN ACETIC ACID SOLUTION

G. Marino
Istituto Chimico-Universita di Trieste, Italy

(*Received* 20 *May* 1964; *in revised form* 25 *November* 1964)

Abstract—The uncatalysed halogenation of thiophene has been examined in acetic acid solution at 25°.

The chlorination of thiophene like that of benzene follows second order kinetics, first order in each reagent, whereas bromination exhibits complex kinetics, with a kinetic order intermediate between two and three.

The thiophene–benzene reactivity ratio k_T/k_B was found to be $1{\cdot}3 \times 10^7$ and $1{\cdot}7 \times 10^9$ for chlorination and bromination, respectively. The reaction products, as shown by vapour-phase chromatographic analysis, were only 2-halothiophene (major component) and 2,5-dihalothiophene. No trace of 3-halothiophene was identified.

The reactivity data are compared with those of other representative benzene derivatives.

INTRODUCTION

Although the reactivity of thiophene towards electrophilic reagents is well known, the difference between thiophene and benzene in their reactivity towards electrophiles has only recently been put on a quantitative basis. Data concerning nitration,[1] mercuration,[1] proto-desilylation[2] and hydrogen-exchange[3,4] have been published in the past few years.

According to the data, the rate of thiophene relative to benzene is much higher in the mercuration (97,000) than in the nitration reaction (850), whereas it has been well established that the former reaction is much less selective than the latter.[5] Also, the directing effects of the substituents differ noticeably from one substitution reaction to another,[6] confirming the view that the mechanism involved for benzene could be different from that for thiophene.

This scarcity of the available quantitative data,[7,8] prompted the present research programme concerning the electrophilic substitution in the thiophene series; in this article a kinetic study of the uncatalysed halogenation of thiophene by molecular chlorine and bromine in glacial acetic acid solution is reported.

The data in the literature on the halogenation of thiophene are only semiquantitative; the relative reactivity of bromination of thiophene with respect to benzene deduced from the kinetic work of Lauer[9] is not reliable, as pointed out in the discussion.

[1] R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari and J. Ogawa, *Nippon Kagaku Zasshi* **78**, 962 (1957); *Chem. Abstr.* **54**, 14224 (1960).

[2] F. B. Deans and C. Eaborn, *J. Chem. Soc.* 2303 (1959).

[3] K. Halvarson and L. Melander, *Arkiv Kemi* **8**, 29 (1955).

[4] B. Oestman and S. Olsson, *Arkiv Kemi* **15**, 275 (1960).

[5] L. M. Stock and H. C. Brown, *Advances in Phys. Org. Chem.* Vol. I, p. 35. Academic Press, London (1963).

[6] S. Gronowitz, *Arkiv Kemi* **13**, 295 (1958).

[7] S. Gronowitz, *Advances in Heterocyclic Chemistry* Vol. I, p. 1. Academic Press, London (1963).

[8] J. Ridd, in A. R. Katritzky, *Physical Methods in Heterocyclic Chemistry* Vol. I, p. 109. Academic Press, London (1963).

[9] K. Lauer, *Ber. Dtsch. Chem. Ges.* **69**, 2618 (1936).

The reaction of thiophene with chlorine, in the absence of solvent, was studied by Hartough *et al.*[10,11] These authors report that, when chlorine is allowed to bubble into thiophene, various substitution- and addition-products are formed, the percentage of the addition products depending upon the experimental conditions and the chlorine–thiophene ratio. Hartough,[12a] however, observed that, when either reactive positions 2 and 5 are unsubstituted, the main reaction is always one of substitution.

As regards bromination, although it was the first reaction of thiophene to be reported,[13] no detailed study of the products was reported until 1957, when Lawassen[14] investigated the reaction products of thiophene with bromine under several experimental conditions; no addition products were isolated.

The rates of chlorination and bromination of thiophene relative to benzene have been studied under conditions similar to those used for benzene[15,16] i.e. in the dark using acetic acid as solvent at 25°.

RESULTS

Chlorination. On account of the reactivity of thiophene, instead of the technique of the multiple withdrawals, the kinetic procedure used for the halogenation of reactive polymethylbenzenes[17] was adopted. This procedure permits concentrations as low as 10^{-4} M and the reaction may be interrupted at 20 second intervals. Therefore, a single determination for a particular chlorine concentration at a given time is obtained from each run. The rate constant is then calculated by application of the proper integrated second-order expression, the dihalogenation step (see page 7) being neglected to a first approximation.[18] The probable error of this method is about 7–8%.

Many runs were carried out at different initial concentrations and quenched at times ranging from 10 to 60% reaction.

As the calculated k values were constant within the probable error ($19{\cdot}0 \pm 1{\cdot}5$ $1\ \text{moles}^{-1}\ \text{sec}^{-1}$); it was concluded that the chlorination of thiophene in acetic acid, like that of benzene and the other benzene derivatives, follows second order kinetics, first order with respect to each reagent.

Since the rate constant for the chlorination of benzene in anhydrous acetic acid has been given as $1{\cdot}52 \times 10^{-6}$,[16] the calculated rate of thiophene relative to benzene is $1{\cdot}25 \times 10^{7}$.

For an independent confirmation, a known mixture of thiophene and mesitylene (for which the rate relative to benzene is known, $3{\cdot}06 \times 10^{7}$,[17]) was allowed to react in acetic acid with insufficient chlorine; the reaction was allowed to proceed to

---

[10] H. L. Coonradt and H. D. Hartough, *J. Amer. Chem. Soc.* **70**, 1158 (1948).

[11] H. L. Coonradt, H. D. Hartough and G. C. Johnson, *J. Amer. Chem. Soc.* **70**, 2564 (1948).

[12a] H. D. Hartough, *Thiophene and Its Derivatives* p. 173. Interscience, New York (1952); [b] p. 201; [c] p. 498.

[13] V. Meyer, *Ber. Dtsch. Chem. Ges.* **16**, 1465 (1883).

[14] S. O. Lawessen, *Arkiv Kemi* **11**, 373 (1957).

[15] H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.* **79**, 1421 (1957).

[16] H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.* **79**, 5175 (1957).

[17] E. Baciocchi and G. Illuminati, *Gazz. Chim.* **92**, 89 (1962).

[18] The rate constant for the chlorination of 2-chlorothiophene at the same temp is $3{\cdot}4\ 1\ \text{moles}^{-1}\ \text{sec}^{-1}$. The details for this experiment will be reported in a subsequent paper dealing with the chlorination and bromination of 2-substituted thiophenes.

completion and the amounts of chlorothiophene and chloromesitylene obtained were determined by vapour-chromatographic analysis of the reaction mixture. The relative velocity of chlorination of thiophene with respect to mesitylene, calculated by applying the usual formula for competing reactions,[19] is 0·45. Based on this value the thiophene–benzene reactivity ratio is $1{\cdot}38 \times 10^7$ which is in good agreement with the direct determination.

Bromination. In contrast to the chlorination reaction, the bromination of benzene and its derivatives exhibits complex kinetics; the over-all order is intermediate between two and three[20–22] and appears to vary as the reaction proceeds. Previous workers,[15,20,23,24] in order to overcome these kinetic difficulties, have based the relative reactivities on the times required for a given reaction percentage (usually 10%) under standardized conditions.

Because of the great difference in reactivity between benzene and thiophene, it is not possible to compare the times required to achieve 10% reaction for these two substrates under similar experimental conditions. Therefore, thiophene and mesitylene were brominated under identical reaction conditions and the rate of thiophene relative to mesitylene was calculated by a ratio of the 10% reaction times. Since the rate of bromination of mesitylene relative to benzene has been previously determined,[15] the derived velocity of thiophene relative to benzene is $1{\cdot}7 \times 10^9$. Also in this case, for an indirect confirmation a competitive bromination of thiophene and mesitylene was carried out. The value k_T/k_M (9·3), obtained from the analysis of the reaction mixture, is in excellent agreement with the value (9·1) obtained from a comparison of the 10% times.

Thiophene was brominated at different reagent concentrations (Table 1) and the over-all kinetic order of the reaction calculated to be 2·6, similar to that observed in the bromination of the homocyclic aromatic compounds.[20–22]

Analysis of the reaction products. Preliminary experiments showed that, under the conditions used for kinetic measurements (very dilute solutions in anhydrous acetic acid, at 25° and in the dark), substitution products were chiefly formed in both the reactions examined. The amount of the addition products was estimated to be below 2–3% by the procedure described in the Experimental. In order to determine the isomer distribution, equimolecular amounts of thiophene and halogen were allowed to react under conditions similar to those used in the kinetic study, the only difference being the higher concentration (10^{-2} M). The reaction products were treated as described in the Experimental and the products were analysed by vapour-phase chromatography using two different stationary liquids. (The gas-chromatographic technique has been used successfully[25] to separate chloro derivatives of thiophene.) The retention times of the various peaks have been compared with those of synthetic samples of mono- and poly-halogeno derivatives of thiophene, prepared according to the methods described in the literature.

---

[19] G. A. Russell, *Competing Reactions* in *Investigation of Rates and Mechanism of Reactions* p. 344. Interscience, New York (1961).

[20] R. W. Robertson, P. B. D. de la Mare and W. G. Johnston, *J. Chem. Soc.* 276 (1943).

[21] P. W. Robertson, *J. Chem. Soc.* 1267 (1954).

[22] R. M. Keefer, A. Ottenberg and L. J. Andrews, *J. Amer. Chem. Soc.* **78**, 255 (1956).

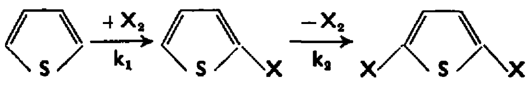
[23] P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.* 1764 (1951).

[24] G. Illuminati and G. Marino, *J. Amer. Chem. Soc.* **78**, 4975 (1956).

[25] E. Profft and G. Solf, *Liebig's Ann.* **649**, 100 (1961).

In both the reactions, the chromatograms of the reaction products exhibit only three peaks: those corresponding to the unreacted thiophene, to the 2-halothiophene and to the 2,5-dihalothiophene. No trace of 3-substituted thiophenes was revealed in the reaction products. The molar percentages of the 2,5-dihalothiophenes were calculated by the aid of calibration curves made up using synthetic mixtures. The values obtained (13% in bromination and 16% in chlorination) indicate that the introduction of the first atom of halogen deactivates the molecule to a smaller extent than in the case of the homocyclic aromatic compounds.

This is an example of a familiar kinetic situation, i.e., the occurrence of two consecutive same-order reactions involving competition for a common reagent.



The ratio k_2/k_1 is derived from the following equation:[26]

$$y^r + y(1 - 2r) + r - 1 = 0$$

where $r = k_2/k_1$ and $y = [\text{dihalothiophene}]_f/[\text{thiophene}]_i$ (subscripts *f* and *i* refer to final and initial concentrations).

The values obtained for the k_2/k_1 ratios, 0·15 for chlorination and 0·14 for bromination, are in good agreement with those derived from a direct comparison of the initial rate constants for thiophene and the corresponding 2-halothiophene.[18] This agreement excludes the possibility that the large amount of dihalothiophene could arise from an insufficient diffusion after the mixing of the reactants due to the very high velocity of the present reactions.

DISCUSSION

The value of the ratio of bromination of thiophene relative to benzene k_T/k_B here reported, $1{\cdot}7 \times 10^9$ is in serious disagreement with the value $2{\cdot}0 \times 10^4$ calculated by Hartough[12b] using the Lauer's data.[14] The discrepancy, however, is essentially due to the reactivity value of benzene reported by Lauer.[27]

It is of interest to compare the reactivity of thiophene with some typical benzene derivatives. Many kinetic studies have been carried out by various authors on the halogenation of activated monosubstituted derivatives of benzene in acetic acid; the kinetic data and the rates relative to benzene have been reported in a recent review.[5] In the reaction with bromine the order of reactivity is the following: diphenyl ether $<$ acetanilide $<$ thiophene $\simeq$ anisole $<$ phenol $<$ N,N-dimethylaniline.

The only data concerning the reaction with chlorine indicate that thiophene is more reactive than both acetanilide and anisole.

An interesting comparison with the reactivities of the polymethylbenzenes (for which the complete series of the relative rates has been determined in both reactions[16,17]), reveals that the reactivity of thiophene is intermediate between that of prehnitene and isodurene in the chlorination reaction and is higher than that of all the polymethylbenzenes (pentamethylbenzene included) in the bromination reaction.

---

[26] P. R. Wells, *J. Phys. Chem.* **63**, 1978 (1959). Cf. also Ref. 19, p. 348.

[27] The bromination of benzene in anhydrous acetic acid is an immeasurably slow reaction; only using 85% aqueous acetic acid (a solvent which provokes an increase in velocity of about 150 times) Brown and Stock[15] were able to follow the real reaction of benzene with bromine. The bromine consumed as observed by Lauer is probably due to the slow reaction of bromine with the solvent.[16]

The relative velocities thiophene–benzene and the isomer distributions (practically 100% of the 2-substituted isomer) provide the partial rate factors (with respect to a position of benzene) for the α-position. The values obtained are $3{\cdot}9 \times 10^7$ and $5{\cdot}1 \times 10^9$ for chlorination and bromination, respectively.

Since no trace of 3-halothiophene was revealed in the reaction mixture, a calculation of the partial rate factors for the β-position is not feasible. Nevertheless, partial rate factors as large as 10^5 for chlorination and 10^7 for bromination are possible for the β-position, since the used analytical technique (VPC using a thermistor-detector) is not able to reveal amounts of 3-halothiophene smaller than 0·2–0·3%.

TABLE 1. TYPICAL KINETIC EXPERIMENTS OF CHLORINATION OF THIOPHENE IN ACETIC ACID AT 25·0°

Concentrations; $M \times 10^4$ Thiophene	Concentrations; $M \times 10^4$ Chlorine	Time sec	Reaction %	k ($1\ \text{mole}^{-1}\ \text{sec}^{-1}$)
4·00	4·00	31	19·25	19·22
6·24	4·00	40	34·80	19·50
8·50	4·10	36	36·50	16·37
4·00	4·00	98	43·50	19·62
6·24	6·24	97	53·20	18·76
6·24	4·00	90	56·50	18·98
5·00	5·00	150	60·80	20·68

TABLE 2. KINETIC DATA OF BROMINATION IN ACETIC ACID, AT 25·0°

Substrate	Concentration, M	10% reaction time, min
Thiophene	0·005	2·46 ± 0·09
Thiophene	0·010	0·78 ± 0·04
Mesitylene	0·005	22·33 ± 0·35

EXPERIMENTAL

Materials. Thiophene (a C. Erba commercial product) was fractionated through a 45-plate Todd column; the intermediate fraction, b.p. 83·8–84° was used for the kinetic study. Glacial acetic acid for freezing point measurements was fractionated, b.p. 116°.

Halothiophenes required as standards for VPC analysis were prepared according to the described methods: 2-chlorothiophene,[11] 2,5-dichlorothiophene,[11] 2-bromothiophene,[12c] 2,5-dibromothiophene,[12c] 3-bromothiophene,[28] 2,3,5-tribromothiophene.[29] The mesitylene used was part of sample made previously.[24]

Kinetic measurements. In accordance with the previous work on benzene derivatives, all the kinetic experiments on halogenation were carried out in a dark room, using a red lamp. The effect of white light on the reaction velocity in the halogenation of thiophene has not been investigated.

The rates of chlorination were measured by using the procedure developed by Baciocchi and Illuminati for very fast reactions.[17] The initial concentration of chlorine was always equal to or smaller than that of thiophene. The results of some typical experiments are reported in Table 1.

Because of the slower reaction rates, bromination was measured using the standard technique.

---

[28] S. Gronowitz, *Acta Chim. Scand.* **13**, 1045 (1959).

[29] J. Rosenberg, *Ber. Dtsch. Chem. Ges.* **18**, 1773 (1885).

Details of the procedure and the analytical method have been described in a previous paper.[24] The times for 10% reaction were evaluated graphically.

Competitive relative rate determinations. Standardized solutions of halogen, mesitylene and thiophene in purified acetic acid were prepared and the reaction started by adding the halogen solution to a stirred solution of the other two reagents immersed in a thermostat bath at 25°. The final concentration of the halogen was always smaller than those of both the aromatic substrates.

The reaction was allowed to proceed to completion; the mixture was poured into excess water and the water extracted 3 times with ethyl ether. The ethereal solution was washed 3 times, dried (Na_2SO_4) and concentrated to small volume. The residue was analysed by vapour phase chromatography employing a C. Erba Vapour Fractometer operated with a 2 m Craig Polyadipate or a 2 m Silicone 301 column at 135 or 145°, using H_2 as carrier gas.

The peaks were easily resolved and identified by comparison with known samples of the various compounds. The areas were measured and the molar ratios among the various components were determined from a calibration curve based on the analysis of synthetic mixtures. The data were employed to calculate the necessary concentration terms in the expression:[19]

$$\frac{k_T}{k_M} = \frac{\lg \frac{T}{T_0}}{\lg \frac{M}{M_0}}$$

where T and T_0, M and M_0 refer to final and initial concentrations ot thiophene and mesitylene, respectively.

Isomer distributions. The isomer distributions were established for reactions carried out at equal concentrations of the reagents (10^{-2} M) and treated as described for competitive experiments in the previous paragraph. The VP chromatographic analysis was performed using the above mentioned stationary phases and the identity of the various peaks was made by the employment of standards. The molar ratios were determined by the use of calibration curves.

Extent of the addition reaction. The reaction mixtures were poured into excess water and the organic material extracted with ether. The ethereal extracts were thoroughly washed with water to eliminate any chloride or bromide ion; the solvent was removed and the residue refluxed with a hydro-alcoholic solution of KOH for 5 hr. The solution was then analysed for the halide ions.

Acknowledgements—The author is grateful to Prof. Illuminati for encouragement and discussion, and to the National Research Council (C.N.R.) for a financial support which made this work possible.