

An analysis on the transmission of electron density through sulphur atoms in the quaternization reactions of benzothiazoles

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Abstract. The kinetics of quaternization of a number of 2-substituted benzothiazoles with alkyl iodides and phenacyl bromide have been studied in nitrobenzene. The order of reactivity of different substituted benzothiazoles has been found to be $-H > NO_2 > Cl$. The relative reactivity of 2-amino and 2-methyl derivatives has been ascribed to a solvation phenomenon. The analysis of rho values from the Hammett equation suggests two possible routes for the transmission of electron density.

Keywords. Quaternization reaction; benzothiazole; Hammett equation.

1. Introduction

In continuation of our earlier studies on reactions on benzothiazole derivatives¹⁻⁷ we report, herein, the quaternization kinetics of some benzothiazoles with alkyl iodides and phenacyl bromide in nitrobenzene medium. The pioneering work of Menschutkin⁸ on the quaternization reaction has initiated a good deal of work with varieties of nucleophiles. Deady⁹, Grob *et al*¹⁰ and Behera *et al*¹¹ have studied the quaternization kinetics of various heterocyclic compounds in different environments. While studying the quaternization kinetics of 2-aminobenzothiazoles with phenacyl bromide, Mishra *et al* have proposed the electron flow from a substituent to the reaction site through sulphur atom². In the present study, an attempt has been made to propose a quantitative approach to the electron flow from the substituent to the reacting nitrogen.

2. Experimental

2.1 Preparation and purification of materials

The preparation of 2-amino benzothiazole and its substituted ones is reported earlier¹¹. 2-Methyl 6-substituted benzothiazoles were prepared by the oxidative cyclisation of appropriately substituted thioacetanilide in presence of hexacyanoferrate¹² (2-methyl 6-nitrobenzothiazole, MP 80°C, yield 70%, Found: N, 14.28%; S, 16.38%, calculated for C₈H₆N₂O₂S, N, 14.4%; S, 16.5%, and 2-methyl 6-chlorobenzothiazole, MP 128°, yield 60%, found: N, 7.54%; S, 17.43%; calculated for C₈H₆NSCl, N, 7.69%; S, 17.6%).

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Phenacyl bromide was synthesised by bromination of acetophenones by the method already reported¹³. All the above compounds prepared were crystallized from alcohol and their homogeneity was checked by tlc on a silica gel plate.

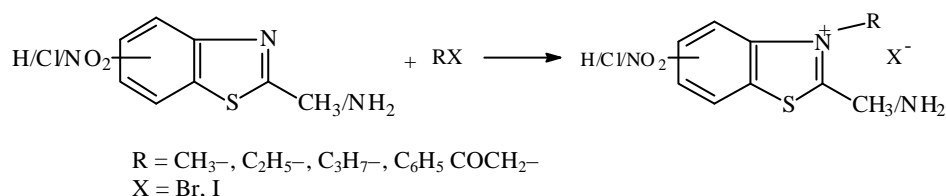
Alkyl iodides were purified by the standard method¹⁴. 2-Methyl benzothiazole was obtained from Schudradt and Co. and was distilled under reduced pressure. Nitrobenzene (AR BDH) was purified and stored in dark¹⁵.

2.2 Kinetic measurement

The method of measuring rate of the reaction has been reported earlier³. Pseudo first-order kinetics were maintained during the course of the kinetic run where the concentration of alkyl halide was around 20 times that of the substrate. The rate data at various temperatures and the values of ΔH^\ddagger and ΔS^\ddagger are given in tables 1 and 2.

3. Results and discussion

The reaction proceeds in the following manner.



The reaction occurs at the ring nitrogen in preference to the exocyclic nitrogen, because of the existence of the charge delocalization over both nitrogens in the manner of an amidinium cation. The transition state for quaternization at the ring nitrogen is more stable than that at the exocyclic nitrogen. Therefore, the kinetic controlled product due to the quaternization at the most basic nitrogen is isolated. It is also known that mono alkylation and protonation of 2-aminopyridine ($pK_a = 7.2$) mainly occurs at the ring nitrogen¹⁶.

The formation of the ions due to quaternization has been followed conductometrically and from the slopes of the linear plots of $\log (R_t/R_\infty - R_t)$ vs time, the values of rate constant have been evaluated and given in tables 1 and 2. With a view to checking the possibility of ion pair formation in nitrobenzene, which would cause an increase in R_∞ value and give erroneous results of rate constants, the values of resistance of very dilute solutions of methiodides were obtained. The linear plot of resistance versus concentration on extrapolation gave the same value of R_∞ at the desired reaction concentration.

Various substituted 2-amino and 2-methyl benzothiazoles were quaternized with methyl iodide and phenacyl bromide. The order of reactivity of the substituents was found to be $-\text{H} > \text{NO}_2 > \text{Cl}$. The substituents at position 2, affect the reaction rate in the order, 2-Me > 2-NH₂ for all the three sets of compounds. This is quite in agreement with earlier observation¹¹. The rate ratio of 2-methyl vs 2-amino compounds is found to be temperature independent. The values of rate ratio are 1.3 for benzothiazole, 2.6 for 6-chlorobenzothiazole and 2.0 for 6-nitrobenzothiazole systems. The values of enthalpy of activation varies between 37 to 64 kJ per mole and those of entropy of activation between -150 joule to -250 joule.

Table 1. Values of rate constants, enthalpy and entropy of activation of quaternization reactions of benzothiazoles with methyl iodide and phenacyl bromide. Values given in parentheses are rate constants determined by argentometric titration.

Compound	Methyl iodide					Phenacyl bromide						
	$(\times 10^5) k s^{-1} \text{ at}$					$(\times 10^5) k s^{-1} \text{ at}$						
	40°C	50°C	60°C	70°C		60°C	70°C	80°C	90°C			
2-Amino benzothiazole	10.7	18.70	36.80	–	52.20	0.152	3.70	5.76	7.96	–	37.08	0.21
2-Methyl benzothiazole	–	22.60	47.20	137.6	52.20	0.155	(3.52)	(5.54)	(7.48)	–	–	–
2-Amino-6-chloro-benzothiazole	0.69	1.37	2.46	3.26	44.27	0.189	0.86	1.46	1.92	2.70	37.70	0.20
2-Methyl-6-chloro-benzothiazole	1.82	3.55	6.50	11.73	55.05	0.163	–	–	–	–	–	–
2-Methyl-6-nitrobenzothiazole	3.30	3.79	5.62	8.76	29.07	0.242	–	–	–	–	–	–
2-Amino-6-nitrobenzothiazole	0.85	1.87	2.82	6.39	33.47	0.235	**	6.52	2.26	4.03	54.07	0.16
								(6.38)	(2.16)	(3.96)		

*Value at 80°C; **value at 100°C

Table 2. Values of rate constants, enthalpy and entropy of activation of the quaternization reaction of benzothiazoles with alkyl iodides.

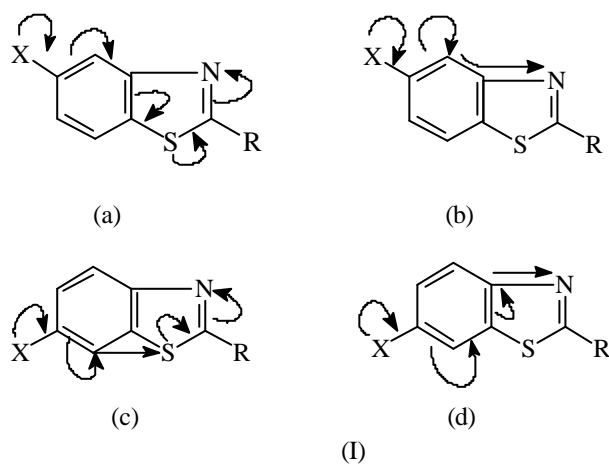
Benzothiazoles	Alkyl iodides	$(\times 10^5) k$ in s^{-1}				ΔH^\ddagger (kJ mole $^{-1}$)	$-\Delta S^\ddagger$ (kJ mole $^{-1}$)
		40°C	50°C	60°C	70°C		
2-Amino benzothiazole	Ethyl iodide	0.037	0.051	0.176	0.199	50.28	0.189
2-Methyl benzothiazole	Ethyl iodide	0.041	0.053	0.085	0.162	63.81	0.158
2-Amino benzothiazole	Propyl iodide	0.015	0.087	0.097	0.142	62.85	0.156
2-Methyl benzothiazole	Propyl iodide	0.192*	0.046	0.066	0.121	45.45	0.211

* $k \times 10^5$ at 80°

The reactivity of nitrogen atom is influenced by the substituent possibly by two paths – one through sulphur atom and the other directly. Both the paths of propagation of electron density for substituents at position 5 and 6 are shown in I for 5- and 6-substituted benzothiazoles. For a similar situation encountered in the alkaline hydrolysis of phthalides, Jaffe¹⁷ has used two reaction constants for the difference in the electron propagation path from the substituent to the reaction site. He has proposed an equation

$$\text{Log } k/k_0 = \mathbf{r}_1 \mathbf{S}_m + \mathbf{r}_2 \mathbf{S}_p, \quad (1)$$

where \mathbf{r}_1 and \mathbf{r}_2 are two different reaction constants for the two different paths of electron propagation from the substituent placed at a position meta and para to the propagation path respectively.



In analogy to Hammett–Jaffe equation, two equations (2) and (3) can be written where \mathbf{r}_5 and \mathbf{r}_6 are the reaction constants for transmission of electron through sulphur or through a direct path and k_5 and k_6 are reaction constant for 5 and 6 substituents

Table 3. Values of r_s and r_d for the reaction of (i) 2-amino benzothiazoles + methyl iodide, (ii) 2-methyl benzothiazoles + methyl iodide, and (iii) 2-amino benzothiazoles + phenacyl bromide.

Reaction	r_s	r_d	$(r_s + r_d)$
(i)	- 2.58	0.92	- 1.66
(ii)	- 6.11	4.37	- 1.74
(iii)	- 0.94	- 0.15	- 1.09

respectively. In I-a (sulphur route) and I-d (direct route) the substituents behave as para substituents in the benzene ring where as in I-b and I-c they behave as meta substituents.

$$\text{Log}k_s/k_H = r_d S_m + r_s S_p, \quad (2)$$

$$\text{Log}k_d/k_H = r_d S_p + r_s S_m. \quad (3)$$

The values of r_s and r_d have been obtained for the reaction of (i) 2-aminobenzothiazoles and methyl iodide, (ii) 2-methylbenzothiazoles and methyl iodide, and (iii) 2-aminobenzothiazoles and phenacyl bromide (table 3). The rho values have been evaluated with a view to see the trend in the changes of rho values in the three sets of reactions. The trends in these values lead to some striking conclusions.

1. There is a greater flow of electron density to nitrogen through sulphur route than through a direct route. Davis *et al*¹⁸ have also indicated substantial transmission of electronic effects through the sulphur atom from the ultraviolet spectral data of some sulphur amides. A mechanism of through-conjugation involving $pP-dP-pP$ conjugation have been suggested for phenyl vinyl sulphides and supported by CNDO/2 calculations¹⁹.
2. The demand of the transition state on the substituent in benzothiazole is more in 2-methyl compounds than in 2-amino compounds. This is quite obvious since an amino group stabilizes the developing positive charge much more than a methyl group does ($S_{p-Me} = -0.31$ and $S_{p-NH_2} = -1.3$).
3. Further in 2-amino compounds the demand of the transition state on the substituents is very much less in the reaction with phenacyl bromide than with methyl iodide. This may be due to the formation of a hydrogen bonded cyclic transition state with phenacyl bromide³.
4. The kinetics of quaternization of 2-methyl benzothiazole has also been followed with ethyl and *n*-propyl iodides in nitrobenzene. The values of rate constants, enthalpy of activation and entropy of activation are given in table 2. The order of reactivity of these alkyl iodides is MeI > EtI > *n*-PrI. This order has also been observed earlier by Deady and Stillman²⁰.

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