BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (2), 604—607 (1979)

Quaternisation at an Sp^2 Nitrogen. II.[1] An Analysis on the Substituent Effect and on the Nature of the Transition State

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(Received August 1, 1977)

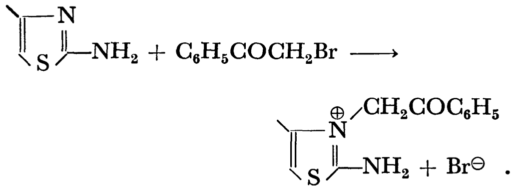
The kinetics of *N*-phenacylation of a number of substituted thiazoles and substituted phenacyl bromides have been investigated in nitrobenzene and in a number of other dipolar aprotic solvents. The rate constants of 2-amino-4-phenylthiazoles and 2-aminobenzothiazoles have been calculated with suitably developed equations. The deviation of the observed values from the calculated results has been ascribed to the steric effect. A seven membered hydrogen bonded transition state has been proposed on the basis of the results obtained from the substituent and medium effect.

In the field of quaternisation reactions pioneering and extensive work have been done by Menschutkin.[2] The reaction has been used successfully in the development and understanding of mechanistic principles. The quaternisation kinetics of pyridines with methyl iodide has been studied by Fischer and Vaughan[3] and Murai *et al.*[4] They observed the operation of normal substituent effect for the substituents at position 4 and a good correlation between the rate constant and pK_a with the exception of $-NH_2$, $-CO-C_6H_5$, $-COOR$, and $-CN$ groups. In an earlier study[5] on the quaternisation of thiazoles, the sulfur atom was observed to act as a resonance transmitter. The lower reactivity of 2-amino group over 2-methyl group was explained as due to the existence of an equilibrium between loose contact pairs and charge transfer complexes.

Deady *et al.*[6] also studied the rate of *N*-methylation of a number of heterocyclic compounds such as *N*-methylpyrazole, isothiazole, isoxazole and their 2 : 1 and 1 : 2 analogues; 2-methyl-benzothiazoles; 2,1,3-benzoxadiazoles; 2,1,3-benzothia (or selena) diazoles; 1,2,5-oxadiazole; and 1,2,5-thiadiazoles. They concluded a reactant-like transition state for the Menschutkin reaction. The present work was undertaken to investigate the nature of the transition state during the course of *N*-phenacylation reaction.

Results and Discussion

The reaction of 2-aminothiazole and phenacyl bromide takes place according to



(A)

The rate data, Arrhenius parameters and the entropy of activation values for this reaction are given in Table 1. The greater rate of reactivity of **5** over **1** is ascribed to the presence of a *p*-OMe group, which stabilizes the transition state by interacting through the sulfur atom. Substantial transmission of electronic effects through the sulfur atom has been clearly shown by Davis *et al.*[7] from the ultraviolet spectral data of some sulfur amides. A mechanism of through conjugation involving p-π, d-π, p-π conjugation has been suggested for phenyl vinyl sulfides[8] and supported by CNDO/2 calculations.[9] Discussions have been made by various workers.[10]

*2-Aminobenzothiazole(**1**), 2-Amino-4-phenylthiazole(**2**), 2-Amino-4,5-diphenylthiazole(**6**), and 2-Aminopyridine(**8**).* Since the sulfur atom acts as a resonance transmitter, it can be considered equivalent to a vinyl group. Therefore, the compounds **1**, **2**, and **6** can be considered equivalent to 2-amino-6-phenylpyridine, 2-aminoquinoline, and 2-amino-5,6-diphenylpyridine, respectively. Considering compound **8** as a standard, the rate constants of **1** and **2** can be calculated by means of

$$k_1(\text{calcd}) = \frac{\beta_s}{\beta_{\text{vinyl}}} \times \frac{K_B(\text{2Ph-pyridine})}{K_B(\text{Pyridine})} \times k_8, \qquad \text{(B)}$$

and

$$k_2(\text{calcd}) = \frac{\beta_s}{\beta_{\text{vinyl}}} \times \frac{K_B(\text{Quinoline})}{K_B(\text{Pyridine})} \times k_8, \qquad \text{(C)}$$

where β_s is the resonance integral of the S atom and the vinyl group, K_B is the basicity constant of base and k_8 is the observed rate constant for compound **8**. The values of k_1 and k_2 at various temperatures and the calculated and observed rate constants are given in Table 3. The ratio falls from 10.0 at 60 °C to 3.0 at 100 °C for compound **1** whereas it changes from 1.5 to 1.3 for compound **2**. The values of energy of activation obtained with the calculated rate constants are 6.45 and 8.64 kcal mol^{-1} as against 13.40 and 9.52 kcal mol^{-1} derived from observed rate constants for compounds **1** and **2**, respectively. The agreement between the observed and calculated rate constants appears reasonable in view of the assumptions: (1) steric effect during the course of protonation and phenacylation is the same and (2) an amino group at 2-position produces the same effect in both the processes. However, for compound **2** a greater divergence is noted than for compound **1**. The discrepancy might be due to the librational freedom of the phenyl group at position 4 in compound **2**. The free libration of the phenyl group becomes restricted during the course of phenacylation due to the steric interaction of ortho hydrogen atom and the phenacyl moiety. Therefore, the plane of the phenyl group will rotate to the thermodynamically favoured conformation, *i.e.*, the planes of the π MO of the phenyl and the thiazole ring will tend to be orthogonal, causing destabilisation of the transition state. Thus the energy of activation

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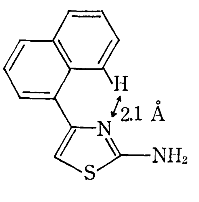
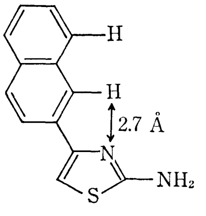
obtained with observed rate constant is much higher with **2** than with **1** as compared to the same obtained from calculated rate constants.

4-(1- and 2)-Naphthylthiazoles. The greater rate of reactivity of 1-naphthyl over 2-naphthyl group at position 4 of the thiazole ring can be ascribed to both steric and electronic factors. The ratio of F_r and Z_r values for position 1 and 2 of the naphthalene are 1.12 and 1.04, respectively.[11] Brown[12] showed a good correlation between F_r and Z_r values with the reactivity parameter, $\sigma_r(\log k/k_0=\sigma_r\rho^*)$ with a deviation $\simeq 6\%$. The ratio of logarithm of rate constants of 4-(1- and 2)-naphthylthiazole is 0.81. Examination of the model shows that H atom at C-8 in I is nearer by 1.3 times to the H atom at C-1 (II). Thus, the ratio of rate constants of 4-(1- and 2)-naphthylthiazole in the absence of the steric effect due to the nearness of C_α–H atom would have been $0.81\times 1.3=1.053$, which is in good agreement with the ratio of F_r and Z_r values. Charton[13] also concluded that E_s parameters are a function of the Van der Waals radii only.

The increased rate of reaction of **6** over **2** can be ascribed to a buttressing effect on the phenyl group at position 4 due to the same group at position 5.

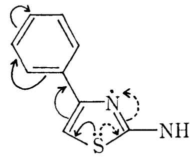


I



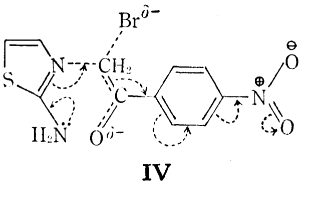
II

The phenyl ring at position 4 interacts with the electron pair of the sulfur atom (III) and the electron density around nitrogen is relatively decreased.[14] The phenyl ring at position 5 decreases this electronic effect by sterically interfering with the group at position 4.



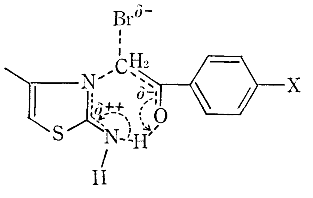
III

Reactivity of Phenacyl Bromide: The order of reactivity of the substituted phenacyl bromide is, m-$NO_2\simeq p$-$NO_2>p$-$Cl>p$-$OMe>$-H (Table 3). The order of reactivity determined earlier by Rout *et al.* in the reaction of phenacyl bromides and aniline is, p-$NO_2>m$-$NO_2>p$-$Cl>$-$H>$-OMe.[15] The greater rate of reactivity of nitrophenacyl bromide over the unsubstituted one is in line with the transition state (IV) proposed by them and other workers[16] for similar reactions.



IV

The transition state is stabilised by an interaction with the $-NH_2$ group (arrows). However, it cannot explain the order of reactivity. If a hydrogen bonded structure (V) is proposed for the transition state then the effect of p-NO_2 and p-OMe groups can be understood: (i) in $X=NO_2$, electron withdrawing effect of

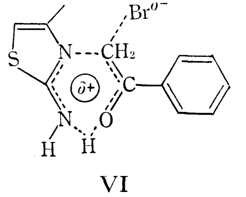


V

NO_2 is lowered by the electron movement shown in the cyclic transition state, (ii) in X=MeO, the electron movement in V is enhanced by electron donating effect of MeÖ. The possibility of such a hydrogen bonded structure is also further confirmed from IR data of 2-amino-3-phenacyl-4-phenyl-3-thiazolium bromide. The >C=O group stretching frequency occurs at 6.1—6.15 μ, whereas in acetophenone it is 5.95 μ. The shift in *o*-hydroxyacetophenone and salicylaldehyde, where chelation has been established is by 0.15 μ. Therefore, these is a case to believe that a hydrogen bonded structure also exists in the quaternary salt.

Medium Effect: With a view to understanding further the nature of the transition state, the *N*-phenacylation kinetics has been studied with 2-aminobenzothiazoles. The order of reactivity in different solvents was observed to be DMA>DMF>NB>BN>AN>BA>CB (Table 4). This is the order of decreasing dielectric constant of the solvents (AN being an exception). A plot of log k *vs.* $(D-1)/(2D+1)$, gives a straight line, AN and NB not lying on the line. This order of reactivity in different solvents also does not conform to the order of Z values[17] and E_T values[17] of these solvents, suggesting a nonquaternary salt-like structure for the transition state. However, there seems to be some correlation with the dipole moment of these solvents. The order of increasing dipole moment of these solvents is BN>NB>DMF>DMA>AN. There is a reversal in the order with respect to the first four solvents. Plots of ΔS^*, ΔH^* *vs.* dipole moment give straight lines whereas similar plots with $(D-1)/(2D+1)$ show a scatter.

On the basis of these evidences, a transition state (VI) is suggested for the phenacylation process of 2-aminothiazoles.



VI

Experimental

4-Substituted 2-aminothiazoles were prepared by condensation of appropriately substituted phenacyl bromide and

Table 1. Values of rate constants at different temperatures, energy of activation and entropy of activation of the quaternisation reaction of some heterocyclic bases and phenacyl bromide in nitrobenzene

Compound No.	Compound	$k\times10^5$, s^{-1}						E kcal mol^{-1}	$-\Delta S^*$ in e.u.
		60 °C	70 °C	75 °C	80 °C	90 °C	100 °C		
1	2-Aminobenzothiazole	3.70	5.69	6.60	7.96	—	—	9.52	42.0
2	2-Amino-4-phenylthiazole	0.20	0.39	—	0.79	1.24	2.09	13.40	35.5
3	2-Amino-4-(1-naphthyl)thiazole	3.36	5.56	6.53	7.87	—	—	12.28	34.2
4[a)]	2-Amino-4-(2-naphthyl)thiazole	—	0.86	1.03	1.27	—	—	9.51	45.6
5[b)]	2-Amino-4-(*p*-methoxyphenyl)thiazole	—	0.80	0.90	1.12	—	—	9.43	45.1
6	2-Amino-4,5-diphenylthiazole	2.63	3.78	4.54	5.78	—	—	9.79	41.8
7[c)]	2-Methylbenzimidazole	12.36	20.04	—	26.92	38.4	—	9.89	38.7
8[d)]	2-Aminopyridine	24.43	30.3	—	34.08	45.6	—	8.91	40.4
9	2-Methylbenzothiazole	1.39	—	3.30	5.50	—	—	11.97	35.7
10[e)]	2-Methylmercaptobenzothiazole	4.97	7.87	—	13.0	—	—	9.86	41.2

a) $k\times10^5$ at 85 °C=1.42. b) $k\times10^5$ at 85 °C=1.27. c) $k\times10^5$ at 65 °C=15.90. d) The data are at 40, 45, 50, and 60 °C, respectively. e) $k\times10^5$ at 50 °C=3.43 s^{-1}.

Table 2. Values of rate constants at different temperatures, energy of activation and entropy of activation of the reaction of 2-amino-4-phenylthiazole and phenacyl bromides in nitrobenzene

Compound	$k\times10^5$ in s^{-1}					E kcal mol^{-1}	$-\Delta S^*$ in e.u.	ΔF^* in kcal mol^{-1}
	60 °C	70 °C	75 °C	80 °C	90 °C			
Phenacyl bromide[a)]	—	0.39	—	0.79	1.24	13.40	35.5	25.5
4-Nitrophenacyl bromide[b)]	1.49	1.9	—	3.80	6.60	11.75	37.1	25.8
4-Chlorophenacyl bromide[c)]	—	0.51	—	1.22	1.91	13.38	34.4	25.5
4-Methoxyphenacyl bromide	0.27	0.33	0.66	0.84	—	13.21	36.0	25.9
3-Nitrophenacyl bromide	1.68	2.01	3.40	3.80	—	9.89	42.6	24.9

a) $k\times10^5$ at 100 °C=1.58 in s^{-1}. b) $k\times10^5$ at 50 °C=0.77 and at 100 °C=13.44 in s^{-1}. c) $k\times10^5$ at 85 °C=1.67 in s^{-1}.

Table 3. Calculated rate constants (k_1 for 2-amino-4-phenylthiazole, k_2 for 2-aminobenzothiazole)

Temp in °C	Calcd $k_1\times10^5$ in s^{-1}	$\frac{k_1\text{ calcd}}{k_1\text{ exptl}}$	E in kcal mol^{-1}	Calcd $k_2\times10^5$ in s^{-1}	$\frac{k_2\text{ calcd}}{k_2\text{ exptl}}$	E in kcal mol^{-1}
60	2.027	10.0		3.7	1.5	
70	2.837	7.0	6.45	5.69	1.4	8.64
80	3.613	4.5		7.96	1.3	
90	4.654	4.0		—	—	
100	5.928	3.0		—	—	

thiourea in ethanol. The thiazoles obtained were crystallised twice from alcohol. The 2-aminothiazoles prepared by this method are 4-phenylthiazole, mp 150 °C (lit,[18] mp 151 °C); 4-(1-naphthyl)thiazole, mp 144 °C (lit,[19] mp 144 °C); 4-(2-naphthyl)thiazole, mp 134 °C (lit,[19] mp 135 °C); 4-(*p*-methoxyphenyl)thiazole, mp 204 °C (lit,[20] mp 204 °C) and 4,5-diphenylthiazole, mp 180 °C. 2-Methylbenzimidazole and 2-aminopyridine were of Couchlight Renal grade. They were crystallised before use. 2-Methylbenzothiazole (Schudart and Co.) was distilled before use.

Phenacyl bromide was synthesised by the bromination of acetophenone.[21] The substituted phenacyl bromides prepared by this method are 4-nitro-, mp 90 °C (lit,[22] mp 91 °C); 4-chloro-, mp 110 °C (lit,[22] mp 110 °C); 4-methoxy-, mp 72 °C(lit,[22] mp 72 °C) and 3-nitro-, mp 95 °C(lit,[22] mp 96 °C).

Purity of all the synthesised compounds has been confirmed by silica gel G TLC plate.

All the solvents used were of BDH grade. Nitrobenzene was purified by the method of Leffek and Matheson,[23] acetonitrile by that of Coetzee,[24] *N,N*-dimethylformamide by that of Hurt and Simpson,[25] 1-butanol by that of Goldschmidt and Mathieson[26] and chlorobenzene by that of Vogel.[27] Benzonitrile was purified by shaking with silica gel and then stirring with calcium hydroxide for two hours. After decantation, it was distilled under reduced pressure. The middle portion was cut and used. *N,N*-Dimethylacetamide was also used after distillation under reduced pressure.

Kinetic Procedure: The method of rate measurement by conductance method is the same as reported.[5] The pseudo first order rate constants ([Base]=0.0025 M and [α-halo-

Table 4. Values of rate constants at different temperatures, energy of activation, entropy of activation of the quaternisation reaction of 2-aminobenzothiazoles with phenacyl bromide in different solvents

No.	Solvent	$k\times10^4$ in $M^{-1}\,s^{-1}$					E in kcal mol^{-1}	$-\Delta S^*$ in e.u.	ΔF^* in kcal mol^{-1}
		60 °C	70 °C	80 °C	90 °C	100 °C			
1	Nitrobenzene (NB)[a]	7.84 (3.7)	11.6 (5.67)	15.16 (7.96)	—	—	9.52	42.2	24.5
2	Acetonitrile (AN)	2.84	3.5	8.1	23.34	—	14.5	29.9	24.39
3	*N*,*N*-Dimethylformamide (DMF)	6.92 (2.74)	10.0 (4.37)	19.0 (9.17)	20.4 (10.7)	—	10.81	41.03	24.58
4	*N*,*N*-Dimethylacetamide (DMA)	4.76 (2.75)	14.64 (6.9)	22.02 (11.12)	— (16.46)	—	16.22	30.36	25.34
5	Benzonitrile (BN)	—	5.62	8.48	11.66	12.5	13.92	32.4	24.61
6	Chlorobenzene (CB)	—	1.54	3.58	5.12	3.5	10.82	44.50	25.81
7	Butyl alcohol (BA)	—	1.76	3.76	8.34	6.96	15.67	30.83	25.84

a) $k\times10^4$ at 75 °C$=13.2$ in $M^{-1}\,s^{-1}$. The rate data in parentheses in DMF, DMA, and NB refer to the first order rate constants ($k\times10^5$ in s^{-1}) by conductometric methods.

ketone]=0.05 M) were calculated from the slopes of the linear plots of log $R_t/(R_t-R_\infty)$ *versus* time, where R_t and R_∞ are the electrical resistances at time '*t*' and infinite time, respectively. The rate constants were reproducible within ±0.2 units.

Since the measurements of rate constants in less polar solvents by the conductance method were less satisfactory, the argentometric method was also adopted. The rate constants by both titrimetric and conductometric methods were compared in a few cases and found to agree well in conformity to the observation made by Jones *et al.*[28] A thermostated solution of phenacyl bromide (0.05 M)and 2-aminobenzothiazole (0.05 M) were mixed and the course of the reaction was studied by pipetting aliquots from the reaction mixture at different intervals of time and estimating [Br⁻] argentometrically. The rate constants were calculated by employing the bimolecular rate equation.

The activation parameters were calculated by using bimolecular rate constants.

Funds for this project were kindly provided by the Council of Scientific and Industrial Research, Government of India.

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