

## Kinetics of the reaction of phenacyl bromide with substituted 2-phenylthiazolidines

P Ananthkrishnanadar\* & T R Prabakaran

Department of Chemistry, Annamalai University,  
Annamalainagar 608 002, Tamil Nadu, India

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The kinetics of the reaction of phenacyl bromide with several 2-(*m*- or *p*-substituted phenyl)thiazolidines have been studied at 30.0°, 35.0° and 43.0°C in ethanol. The reaction follows second order kinetics, first order in each reactant. Electron-releasing substituents in SPT facilitate the reaction, whereas electron-withdrawing substituents have a retarding effect. The correlation with  $\sigma$  values yields a better  $\rho$  value of -1.93 at 43.0°C. A similar correlation at 30.0°C provides a  $\rho$  value of -1.14. From the Bronsted plot the value of  $\alpha = 0.91$  is obtained. There is evidence for a triangular transition state in the reaction.

Thiazolidine ring system forms part of medicinally important compounds like penicillin. Bactericidal, fungicidal, antihistamine, antiinflammatory and antiradiation properties are associated with thiazolidine derivatives<sup>1</sup>. N-Substituted thiazolidines are relatively stable and they possess anaesthetic and antileukemic properties<sup>2</sup>. The present investigation assumes importance in view of the pharmacological activities of the products formed in the reaction studied. Although considerable attention has been paid to the reactions of  $\omega$ -bromoketones with nucleophiles such as naphthoate<sup>3-5</sup>, benzoate<sup>6</sup> and phenoxyacetate ions<sup>7</sup> and aniline<sup>8</sup>, there is no report on the kinetics of the reaction of phenacyl bromide (PB) with 2-(*m*- or *p*-substituted phenyl)thiazolidines (SPT). In order to study the reactivity of SPT towards  $\alpha$ -halogeno ketones and also to test the applicability of Hammett equation to a number of reactions involving 2-phenylthiazolidines the title investigation is undertaken.

### Experimental

All the SPT were prepared by Tsukerman's<sup>9</sup> general procedure. Their purities were ascertained by microanalysis and TLC. Pure ethanol was prepared by literature method using diethyl phthalate instead of diethyl succinate. PB was prepared and purified by literature method.

### *pK<sub>a</sub>* measurement

The *pK<sub>a</sub>* of the conjugate acids of the various SPT were determined from *pH* values at half neutralization employing glass electrode. The values are given in Table 1.

### Rate measurement

The kinetic procedure was similar to that employed previously<sup>8</sup>. The rate constants were calculated using the appropriate second order rate equation when two moles of SPT are consumed per mole of phenacyl bromide.

### Products

Standard solutions of appropriate SPT and PB in ethanol were mixed in the ratio 4:1 and maintained at the kinetic temperature until completion. After concentrating the solution to small volume under reduced pressure, the products precipitated were collected, made alkaline and recrystallized. In all the cases only  $\omega$ -2-(*m*- or *p*-substituted phenyl)thiazolidinoacetophenone was formed. No other product was detected. Table 2 lists the compounds isolated, their m.p. and elemental analysis.

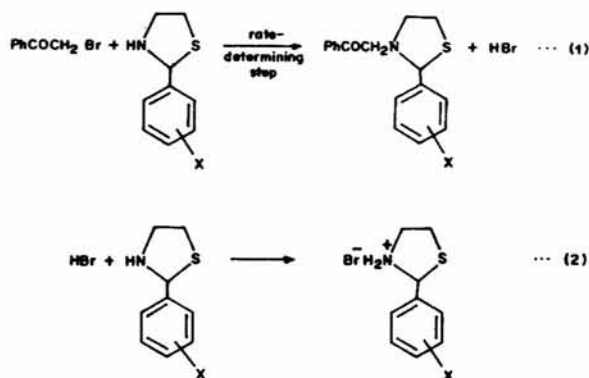
### Results and discussion

Although a number of reactions involving  $\omega$ -halogeno ketones and different nucleophiles have been studied in our laboratories<sup>3-8</sup>, the title reaction assumes significance because there are two centres in SPT, viz., the secondary nitrogen and the sulphur which can act as nucleophiles. But the product studies show that the nitrogen alone selectively behaves like nucleophile.

The reaction is found to be first order in each of the reactants. This was established by usual procedure. Hence, the reaction involves a bimolecular rate-determining stage.

Table 1—The *pK<sub>a</sub>* values of 2-(*m*- or *p*-substituted phenyl)thiazolidinium ions in water at 27.0°C

Substituent	<i>pK<sub>a</sub></i>	Substituent	<i>pK<sub>a</sub></i>
H	5.20	<i>p</i> -OH	5.50
<i>p</i> -CH <sub>3</sub>	5.35	<i>p</i> -Cl	5.01
<i>p</i> -OCH <sub>3</sub>	5.45	<i>m</i> -OH	5.20
<i>m</i> -CH <sub>3</sub>	5.26	<i>p</i> -NO <sub>2</sub>	4.55
<i>p</i> -Br	5.05		



The kinetic data are presented in Table 3. Electron-releasing substituents facilitate the reaction while electron-attracting substituents retard the reaction. The entropy of activation is not constant in the series. A linear relationship between the enthalpies and the entropies of activation exists. As explained by Exner<sup>10,11</sup>, the isokinetic relation-

ship has been examined through a plot of  $\log k_1$  versus  $\log k_2$  where  $k_1$  and  $k_2$  refer to the rate constants at temperatures  $T_1$  and  $T_2$  respectively with  $T_1 > T_2$ . From the slope of the plot, the isokinetic temperature ( $\beta$ ) is calculated to be 306 K when  $T_1 = 308/316$  and  $T_2 = 303$  K.

The plot of  $\log k/k_0$  at 43.0°C against  $\sigma$  constants is linear. The  $\rho$  value is  $-0.76$  at 43.0°C (excluding the result for *m*-OH). The correlation coefficient is 0.947 showing satisfactory fit. However, the correlation improves much giving  $\rho = -1.93$ ,  $r = 0.988$ , when *p*-OCH<sub>3</sub> and *m*-OH groups are eliminated ( $\psi = 0.18$ ). The removal of *m*-OH, *p*-OH and *p*-OCH<sub>3</sub> groups is justified due to their involvement in intramolecular association of the groups in SPT<sup>12</sup>. Our crystal structure studies<sup>13</sup> of SPT indicate that the benzene ring is nearly perpendicular to the thiazolidine ring. The *p*-NO<sub>2</sub> group makes an angle of 4.99° with the least squares plane of the phenyl ring. This disposition of the *p*-NO<sub>2</sub> group offers steric

Table 2—Melting points and elemental analysis of  $\omega$ -2-(*m*- or *p*- substituted phenyl) thiazolidinoacetophenones

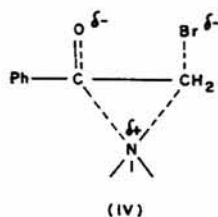
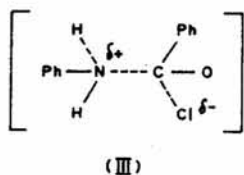
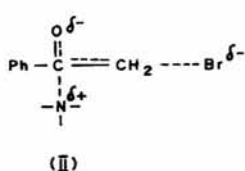
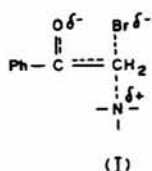
Substituent	Formula	m.p., °C	Calc. %		Found %	
			C	H	C	H
H	C <sub>17</sub> H <sub>17</sub> NOS	78-82	72.08	6.01	71.90	6.19
<i>p</i> -CH <sub>3</sub>	C <sub>18</sub> H <sub>19</sub> NOS	86-87	72.73	6.40	72.63	6.38
<i>p</i> -OCH <sub>3</sub>	C <sub>18</sub> H <sub>19</sub> NO <sub>2</sub> S	90-91	69.01	6.07	69.12	6.18
<i>m</i> -CH <sub>3</sub>	C <sub>18</sub> H <sub>19</sub> NOS	76-77	72.73	6.40	72.74	6.38
<i>p</i> -Br	C <sub>17</sub> H <sub>16</sub> BrNOS	78-79	56.35	4.42	56.30	4.35
<i>p</i> -OH	C <sub>17</sub> H <sub>17</sub> NO <sub>2</sub> S	92-93	68.63	5.69	68.12	5.55
<i>p</i> -Cl	C <sub>17</sub> H <sub>16</sub> ClNOS	95-98	64.25	5.04	64.32	4.98
<i>m</i> -OH	C <sub>17</sub> H <sub>17</sub> NO <sub>2</sub> S	100-101	68.23	5.69	68.19	5.70
<i>p</i> -NO <sub>2</sub>	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S	118-119	62.20	4.88	62.17	4.85
<i>m</i> -Br	C <sub>17</sub> H <sub>16</sub> BrNOS	80-81	56.35	4.42	56.30	4.38

(All compounds crystallized from methanol)

Table 3—Second order rate constants and activation parameters for the reaction between 2-(*m*- or *p*- substituted phenyl)thiazolidines and phenacyl bromide

[SPT] =  $4.00 \times 10^{-2}$  mol dm<sup>-3</sup>; [PB] =  $1.00 \times 10^{-2}$  mol dm<sup>-3</sup>; Solvent: Ethanol (pure)

Substituent	$k_2 \times 10^3$ (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )			<i>E<sub>a</sub></i>	$\Delta H^\ddagger_{316}$	$\Delta S^\ddagger_{316}$
	30.0°	35.0°	43.0°C			
<i>p</i> -CH <sub>3</sub>	4.86	6.19	12.53	57.14	54.51	-108.81
<i>p</i> -OCH <sub>3</sub>	4.51	6.79	10.24	47.87	55.24	-139.93
<i>m</i> -CH <sub>3</sub>	3.47	6.38	13.96	80.74	78.15	-33.21
<i>p</i> -Br	2.32	2.96	6.87	65.87	63.28	-86.13
H	2.28	4.86	10.10	84.80	82.21	-23.06
<i>p</i> -OH	1.71	3.89	22.02	152.47	149.83	197.54
<i>p</i> -Cl	1.48	2.50	8.45	104.80	102.17	38.76
<i>m</i> -OH	1.32	2.41	3.10	47.29	44.65	-151.67
<i>p</i> -NO <sub>2</sub>	0.96	1.39	2.13	46.91	44.28	-155.97
<i>m</i> -Br	0.77	3.65	5.61	108.23	105.60	46.16



hindrance in the transition state. Hence its removal from the correlation is very much justified. Similar plot at 30.0°C provides  $\rho$  as  $-1.14$  (excluding *p*-OH and *p*-NO<sub>2</sub>) with correlation coefficient 0.913. There is considerable scatter of points at 35.0°C in the Hammett plot. This may be due to the isokinetic temperature being close to 35.0°C.

Depending on the mode of attack of the nucleophiles one may consider transition states (I) and (II) in this reaction. The formation of (II) may require very large negative  $\rho$  values. The  $\rho$  value reported earlier<sup>14</sup> for the reaction of substituted anilines and benzoyl chloride in benzene is  $-3.21$  at 25.0°C. The large negative  $\rho$  value for the effect of substituents in aniline is suggestive of very polar activated complex (III) with the extensive formation of the N-C bond.

In the reaction of substituted phenyl chloromethyl sulphides with aniline in dimethylformamide, Ananthakrishna Nadar and Murugesan<sup>15</sup> observed a  $\rho$  value of  $-0.84$  at 40.0°C. In that reaction aniline can attack only the methylene carbon directly. The  $\rho$  values of  $-1.14$  and  $-1.93$  observed in the present study at 30.0° and 43.0°C respectively may suggest the involvement of the triangular transition state (IV) in the reaction.

### Brönsted relationship

The Brönsted equation has been widely employed in numerous general acid-base catalysis reactions<sup>16</sup>. The equation has been shown to be of great importance in the study of nucleophilic reactions<sup>17-19</sup>. The  $\log k$  values of the reaction at 43.0°C are plotted against the  $pK_a$  values in water at 27.0°C of the conjugate acids of SPT used. A good correlation is obtained with  $\alpha = 0.91$  ( $r = 0.936$  excluding *m*-OH). From the significance attached to  $\alpha$ , it may be concluded that there is extensive bonding in the transition state.

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