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# SUBSTITUENT EFFECTS ON THE ADDITION OF ALCOHOLS AND ANILINES TO ORGANIC ISOTHIOCYANATES*

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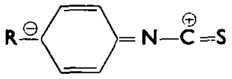
**Abstract**—The addition reactions of alcohols, ROH ($R = CH_3$, $C_2H_5$ n-$C_3H_7$, i-$C_3H_7$ and t-$C_4H_9$), to *p*-bromophenylisothiocyanate show that the rates decrease in the order, $CH_3OH > C_2H_5OH >$ n-$C_3H_7OH >$ i-$C_3H_7OH >$ t-$C_4H_9OH$, although the basicities of the alcohols vary in the reverse order. The results indicate the greater importance of steric factors as compared with polar factors. Evidence is also presented for the formation of a complex between the isothiocyanate and the alcohol in the first stage of the addition reaction.

In the addition of aniline to substituted phenylisothiocyanates the rate data give a satisfactory linear correlation with Hammett $\sigma$ constants and the results clearly show that electron-withdrawing groups favour the addition reaction. The addition of aniline to alkyl isothiocyanates have been studied in order to find out the nature of alkyl group interaction in these derivatives. Kinetic studies on the addition of substituted anilines to phenylisothiocyanate show that the rate of reaction increases with the electron-donating ability of the substituents on the aniline as also the basicity of the aniline.

## INTRODUCTION

RECENTLY, Rao and Venkataraghavan[1] have shown that in the addition of alcohols to substituted phenylisothiocyanates, electron-withdrawing groups in *p*- or *m*-positions favour the reaction and that this is catalysed by triethylamine. Based on kinetic and I.R. data they have proposed that the most prominent resonance form of the *p*-substituted phenylisothiocyanates is I. In this communication, we report the kinetics and energetics of the addition of various alcohols ($R = CH_3$, $C_2H_5$, n-$C_3H_7$, i-$C_3H_7$ and t-$C_4H_9$) to *p*-bromophenylisothiocyanate.



I

The addition of amines to isothiocyanates is generally much faster than addition of the corresponding alcohols. Amines like n-butylamine[2] and piperidine[3] react rapidly

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* Material taken from the Ph.D. thesis of R. Venkataraghavan submitted to the Indian Institute of Science under the guidance of C. N. R. Rao

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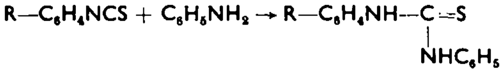
[1] C. N. R. Rao and R. Venkataraghavan, *Tetrahedron* **18**, 531 (1962).

[2] S. Siggia and J. G. Hanna, *Analyt. Chem.* **20**, 1084 (1948).

[3] R. Venkataraghavan and C. N. R. Rao, *Chemist-Analyst* **51**, 48 (1962).

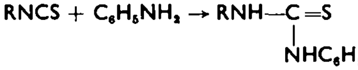
with organic isothiocyanates but aniline being a weaker base reacts with measurable rates. We have now investigated the kinetics and energetics of the addition of aniline to substituted phenylisothiocyanates with a view to study the electrical effects of the substituents R on the benzene ring. Addition of aniline to alkyl isothiocyanates



$$R{-}C_6H_4NCS + C_6H_5NH_2 \rightarrow R{-}C_6H_4NH{-}\underset{NHC_6H_5}{\underset{|}{C}}{=}S$$

(R = *p*-substituents)

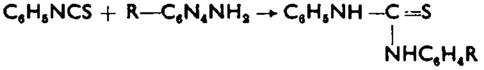
has been studied in order to find out the nature of alkyl group interaction. The dependence of these nucleophilic addition reactions on the basicity (nucleophilicity)



$$RNCS + C_6H_5NH_2 \rightarrow RNH{-}\underset{NHC_6H_5}{\underset{|}{C}}{=}S$$

(R = alkyl group)

of the nucleophilic reagent has been explained by studying the addition of various *p*-substituted anilines to phenylisothiocyanate.



$$C_6H_5NCS + R{-}C_6N_4NH_2 \rightarrow C_6H_5NH{-}\underset{NHC_6H_4R}{\underset{|}{C}}{=}S$$

(R = *p*-substituents)

## RESULTS AND DISCUSSION

### *Effect of substituents on the alcohols*

Table 1 and Fig. 1 clearly show that there is no simple linear relationship between the rate data and the Taft $\sigma^*$ constants.[4] The energies of activation do not vary linearly with $\sigma^*$ constants of the alkyl groups, but vary in proportion to the entropies of activation.[1,5]

The log $k/k_0$ values bear no linear relationship to the $\sigma^*$ constants, noting the

TABLE 1. FIRST-ORDER RATE DATA FOR THE ADDITION OF VARIOUS ALCOHOLS (ROH) TO *p*-BROMOPHENYLISOTHIOCYANATE

| R | Taft $\sigma^*$ of R | Temp. °K | $k$, sec$^{-1}$ $\times 10^5$ | Energy of activation E, k.cal. mole$^{-1}$ | Entropy of activation $\Delta S$ cal. deg.$^{-1}$ at 326·5°K |
|---|---|---|---|---|---|
| $CH_3$ | 0·00 | 326·5 | 9·46 | 15·2 | −29·9 |
| | | 316·5 | 4·49 | | |
| $C_2H_5$ | −0·10 | 326·5 | 5·30 | 15·6 | −29·8 |
| | | 316·5 | 2·42 | | |
| n-$C_3H_7$ | −0·115 | 326·5 | 4·32 | 20·3 | −15·7 |
| | | 316·5 | 1·60 | | |
| i-$C_3H_7$ | −0·190 | 326·5 | 1·29 | 24·0 | −6·7 |
| | | 316·5 | 0·39 | | |
| t-$C_4H_9$ | −0·30 | 352·0 | 0·70 | 26·3 | −6·9* |
| | | 335·0 | 0·10 | | |

* Calculated by using the extrapolated value of the rate constant at 326·5°K

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[4] R. W. Taft Jr., in *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) John Wiley, New York (1956).

[5] J. E. Leffler, *J. Chem. Phys.* **23**, 2199 (1955).

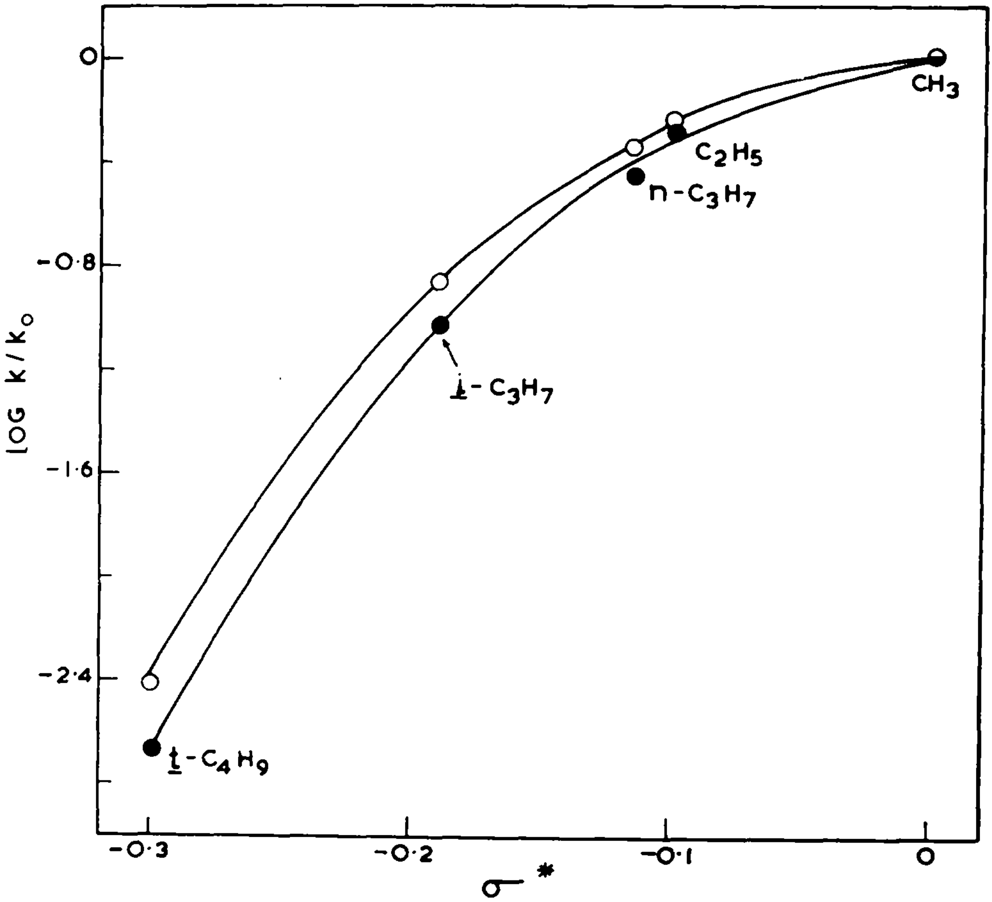

Fig. 1. Correlation of the first-order rate data with Taft $\sigma^*$ constants of alkyl groups.

fact that the acidities of aliphatic alcohols are linearly related to the $\sigma^*$ of the substituents.[6] As the rate of addition decreases in the order, $CH_3 > C_2H_5 > n\text{-}C_3H_7 > i\text{-}C_3H_7 > t\text{-}C_4H_9$, even though the basicity or nucleophilicity of the alkoxide actually varies in the opposite direction, there must be other factors determining the addition of alcohols to isothiocyanates. Although the greater nucleophilicity of the t-butoxide ion would favour the reaction compared to that with methoxide, it is possible that the greater bulk of the t-butoxide group may not act in the same direction. Since the bulk of the alkyl groups increases in the order, $CH_3 < C_2H_5 < n\text{-}C_3H_7 < i\text{-}C_3H_7 < t\text{-}C_4H_9$, it is likely that steric factors also control the rate of addition of alcohols to isothiocyanates. Steric effects may operate in the very initial stage of the mechanism involving the solvation of the isothiocyanate by the alcohol molecules. The first step in the mechanism may involve the formation of a complex between the isothiocyanate and alcohol molecules and the second step involving the breaking up of the solvated isothiocyanate molecule by a second molecule of alcohol.

Ultraviolet absorption data show a dependence of the absorption spectrum of

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[6] J. Hine and M. Hine, *J. Amer. Chem. Soc.* 74, 5266 (1952).

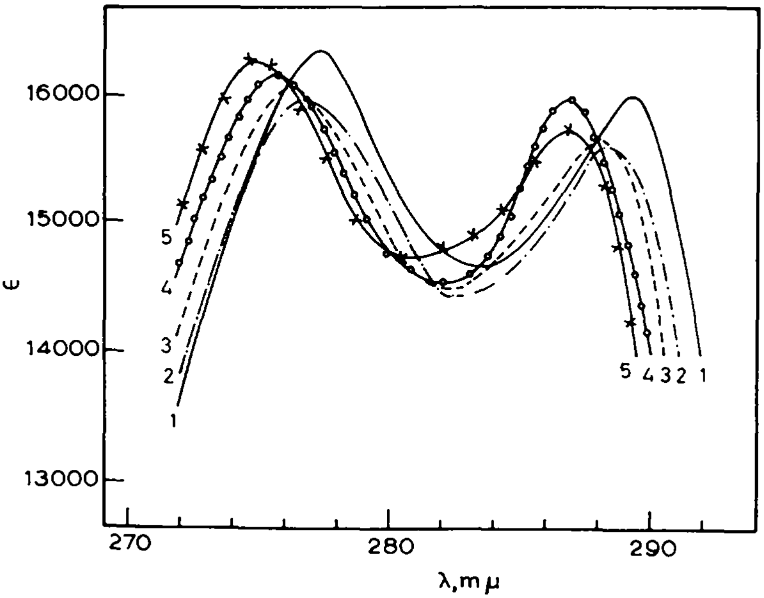

FIG. 2. Near ultraviolet absorption spectra of *p*-bromophenylisothiocyanate in cyclo hexane + isopropanol mixtures: 1, 0%; 2, 20%; 3, 40%; 4, 60%; 5, 80% by volume of isopropanol.

*p*-bromophenylisothiocyanate on the concentration of alcohol (Fig. 2), suggesting a possible equilibrium between complexed and free species of the isothiocyanate which has also been proposed by Baker and Gaunt.[7] In the reactions of alcohols with isothiocyanates steric factors predominate and eclipse the polar effects of the alkyl groups. Baker and Gaunt[7] have found evidence for the competition between the two factors in the case of the addition of alcohols to isocyanates where they find that the rates vary in the order, $CH_3 < C_2H_5 > i\text{-}C_3H_7 \gg t\text{-}C_4H_9$. The trend noticed by us with different alcohols is similar to that found by Djerassi *et al.*[8]

As the kinetic investigations have all been carried out in excess of alcohol in the first-order fashion, it is possible that there are considerable solvent effects in addition to the substituent effects when different alcohols are used. A true picture could be obtained by a study of second-order rates of the addition reactions, but the slow rates of these reactions and the limited temperature range precluded such a study.

In an attempt to compare the relative reactivity of isothiocyanates with nucleophilic reagents, the reactions of phenylisothiocyanate with aniline and phenol were studied. While the reaction with aniline is fast (II order rate constant at 40° = $6{\cdot}25 \times 10^{-4}$ g mole$^{-1}$ l. sec$^{-1}$) there is no measurable reaction with phenol even after twenty hours under the same experimental conditions. These results indicate that the relation of nucleophilicity of the reagents with the reactivity are governed by the same factors as in substitution reactions.[9–11]

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[7] J. W. Baker and J. Gaunt, *J. Chem. Soc.* 19 (1949).

[8] C. Djerassi, *Optical Rotatory Dispersion, Application to Organic Chemistry* p. 144, McGraw-Hill New York (1959).

[9] G. F. Smith, *J. Chem. Soc.* 521 (1943).

[10] C. G. Swain and C. B. Scott, *J. Amer. Soc.* **75**, 141 (1953).

[11] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.* **84**, 16 (1962).

## *Addition of aniline to* p-*substituted phenylisothiocyanates*

TABLE 2. SECOND-ORDER RATE DATA FOR THE ADDITION OF ANILINE TO SUBSTITUTED PHENYLISOTHIOCYANATES ($R—C_6H_4NCS$)

| Substituent R | Hammett $\sigma$ of R | Temp. °K | $k$, g mole$^{-1}$ l. sec$^{-1}$ × $10^4$ | Energy of activation E, k.cal. mole$^{-1}$ | Entropy of activation ΔS cal. deg$^{-1}$ at 313°K |
|---|---|---|---|---|---|
| $p$-Br | 0·232 | 303 | 22·00 | 2·4 | −63·0 |
| | | 313 | 25·00 | | |
| H | 0·000 | 303 | 3·53 | 10·5 | −39·7 |
| | | 313 | 6·25 | | |
| $p$-$CH_3$ | −0·170 | 303 | 1·94* | 9·81 | −43·3 |
| | | 313 | 3·31 | | |
| $p$-$OCH_3$ | −0·215 | 303 | 1·30 | 8·6 | −48·0 |
| | | 313 | 2·07 | | |

* Calculated by using the extrapolated value of log $k/k_0$

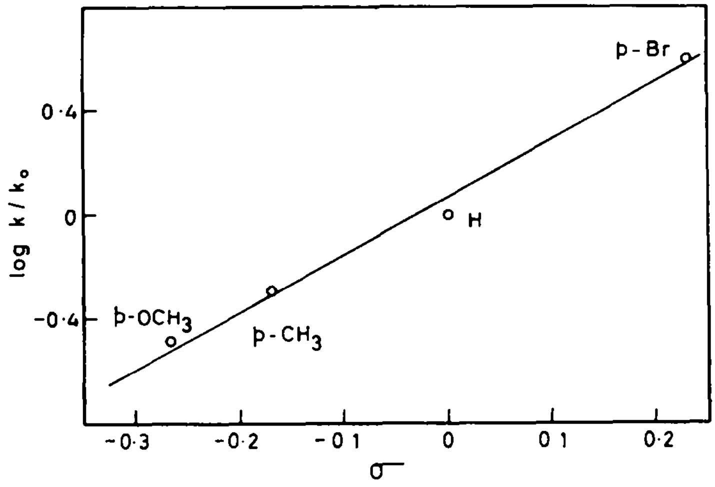

FIG. 3. Correlation of the second-order rate data on the addition of aniline to phenylisothiocyanates with Hammett $\sigma$ constants of $p$-substituents.

The addition reaction of aniline to phenylisothiocyanates is a second-order reaction and is catalysed by triethylamine.[1] Referring to Table 2 and Fig. 3[12] the equation for the least-square line is found to be:

$$\log k/k_0 = 0{\cdot}071 + 2{\cdot}133\sigma \qquad (1)$$

The correlation coefficient and standard deviation are 0·994 and 0·061 respectively and are satisfactory. The kinetic data (Fig. 3) clearly show that electron-withdrawing groups favour the addition of aniline to isothiocyanates.[1,13] Obviously, the most

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[12] D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

[13] G. L. Caldow and H. W. Thompson, *Spectrochim. Acta* **13**, 212 (1958).

prominent resonance form of substituted phenylisothiocyanates (I) is favoured since the products of aniline are thioureas.

The energies of activation listed in Table 2 do not vary systematically with the Hammett $\sigma$ substituent constants. However, the entropies of activation calculated from the absolute rate theory vary linearly with the energies of activation (correlation coefficient of the least-square line = 0·982), indicating that a special case of the Hammett equation[5] is applicable in this case. A similar observation has also been made in the case of addition of alcohols to phenylisothiocyanates.[1]

## *Addition of aniline to alkyl isothiocyanates*

TABLE 3. SECOND-ORDER RATE DATA FOR THE ADDITION OF ANILINE TO ALKYL ISOTHIOCYANATES (R–NCS)

| Substituent R | Taft $\sigma^*$ of R | Temp. °K | $k$, g mole$^{-1}$ l. sec$^{-1}$ $\times 10^4$ | Energy of activation E, k. cal. mole$^{-1}$ | Entropy of activation $\Delta S$ cal. deg$^{-1}$ at 327·5° K |
|---|---|---|---|---|---|
| $CH_3$ | 0·00 | 317·5 | 1·83 | 4·9 | −60·3 |
| | | 327·5 | 2·33 | | |
| $C_2H_5$ | −0·10 | 317·5 | 0·55 | 11·2 | −43·1 |
| | | 327·5 | 0·95 | | |
| i-$C_3H_7$ | −0·19 | 317·5 | 0·18 | 14·1 | −36·0 |
| | | 327·5 | 0·35 | | |
| t-$C_4H_9$ | −0·30 | 317·5 | 0·06 | 9·7 | −52·0 |
| | | 327·5 | 0·09 | | |
| $C_6H_5CH_2$ | 0·26 | 317·5 | 7·40 | 5·1 | −52·5 |
| | | 327·5 | 9·50 | | |

The equation for the least-square line is found to be,

$$\log k/k_0 = 4\cdot139\sigma^* - 0\cdot172 \qquad (2)$$

with the correlation coefficient and standard deviation of 0·987 and 0·155 respectively (Fig. 4). Since the correlation is not satisfactory it may be assumed that the alkyl groups are interacting through hyperconjugation. Assuming that only C—H hyperconjugation is operative in addition to the inductive effect, the Kreevoy–Taft relation,[14]

$$\log k/k_0 = (\textstyle\sum\sigma^*)\rho^* + \Delta nh \qquad (3)$$

was applied to these rate data. $\Delta n$ is the difference in the number of $\alpha$-hydrogen atoms actually available for C—H hyperconjugation compared with the maximum number of three in the case of methylisothiocyanate and h, the hyperconjugation constant. The best value of hyperconjugation constant, h, is found to be 0·13. The least-square line is given by,

$$\log k/k_0 - 0\cdot13\,\Delta n = 3\cdot616\sigma^* - 0\cdot029 \qquad (4)$$

with a correlation coefficient of 0·998 and a standard deviation of 0·05 (Fig. 5). As this is an improvement over the relation obtained merely with $\sigma^*$ constants

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[14] M. M. Kreevoy and R. W. Taft Jr., *J. Am. Chem. Soc.* **77**, 5590 (1955)

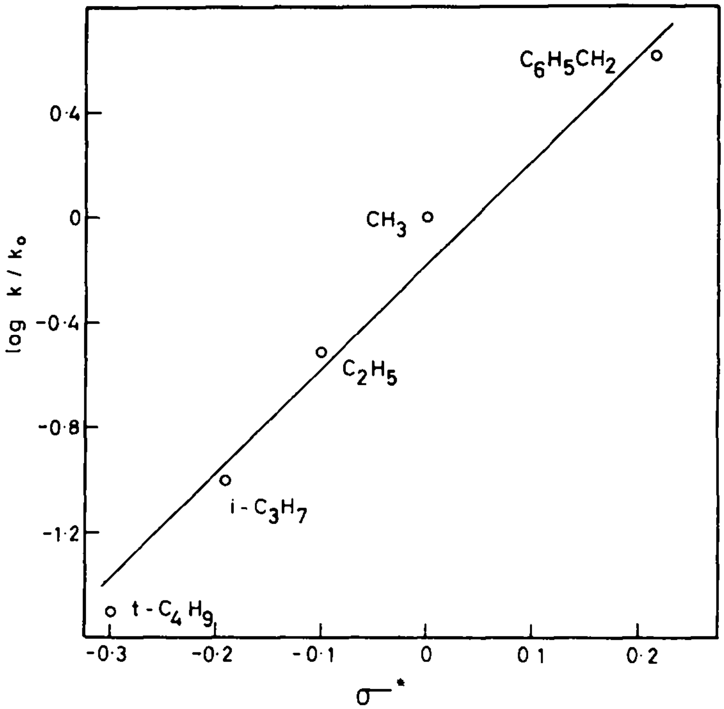

FIG. 4. Correlation of the second-order rate data on the addition of aniline to alkyl isothiocyanates with Taft $\sigma^*$ constants of alkyl groups.

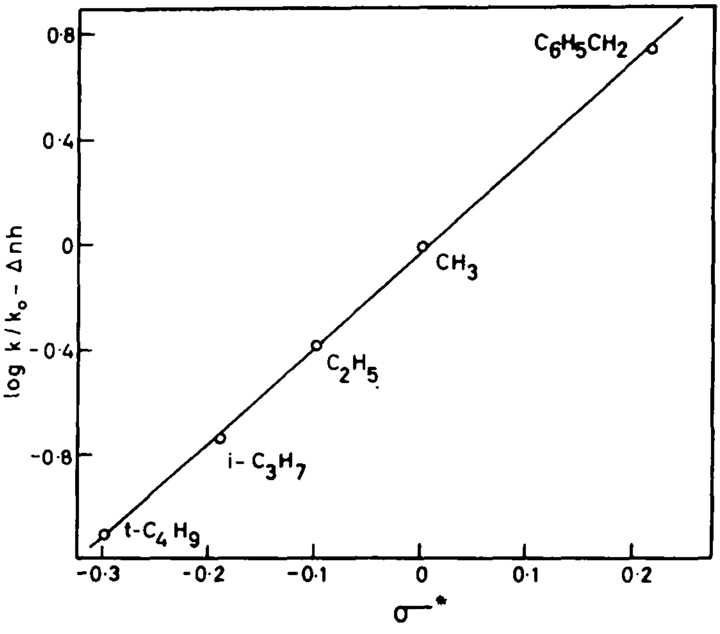

FIG. 5. Plot of ($\log k/k_0$ — Δnh) *versus* Taft $\sigma^*$ constants of alkyl groups.

(Eq. 2, Fig. 4). It may be suggested that inductive and hyperconjugation contributions of alkyl groups are additive as required by the equation 3 of Kreevoy and Taft.[14]

The energies of activation for the addition of aniline to alkyl isothiocyanates (Table 3) do not vary systematically with the $\sigma^*$ substituent constants, but show an approximate linear relationship with the corresponding entropies of activation (correlation coefficient of the least-square line = 0·916).

### *Addition of substituted anilines to phenylisothiocyanates*

TABLE 4. SECOND-ORDER RATE DATA FOR THE ADDITION OF SUBSTITUTED ANILINES ($R—C_6H_4NH_2$) TO PHENYLISOTHIOCYANATE

| Substituent R | Hammett $\sigma$ of R | Temp. °K | $k$, g mole$^{-1}$ l. sec$^{-1}$ $\times 10^4$ | Energy of activation E, k.cal. mole$^{-1}$ | Entropy of activation ΔS cal. deg$^{-1}$ at 313°K |
|---|---|---|---|---|---|
| *p*-Br | 0·232 | 313 | 0·63 | 5·5 | −60·2 |
| | | 327·5 | 0·95 | | |
| H | 0·000 | 303 | 3·53 | 10·5 | −39·7 |
| | | 313 | 6·25 | | |
| *p*-$CH_3$ | −0·170 | 303 | 14·50 | 15·1 | −21·7 |
| | | 313 | 32·90 | | |
| *p*-$OCH_3$ | −0·268 | 303 | 93·00 | 3·6 | −56·1 |
| | | 313 | 113·00 | | |

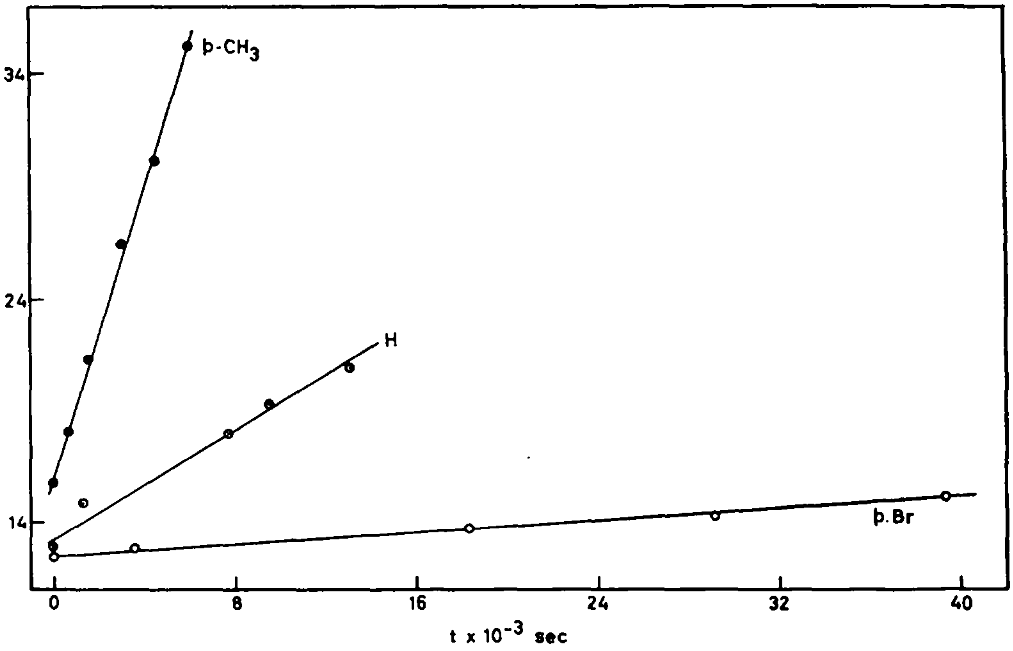

FIG. 6. Kinetics of the addition of *p*-substituted anilines to phenylisothiocyanates at 40°C in presence of triethylamine catalyst (0·01 M) c = Concentration of isothiocyanate in moles per litre.

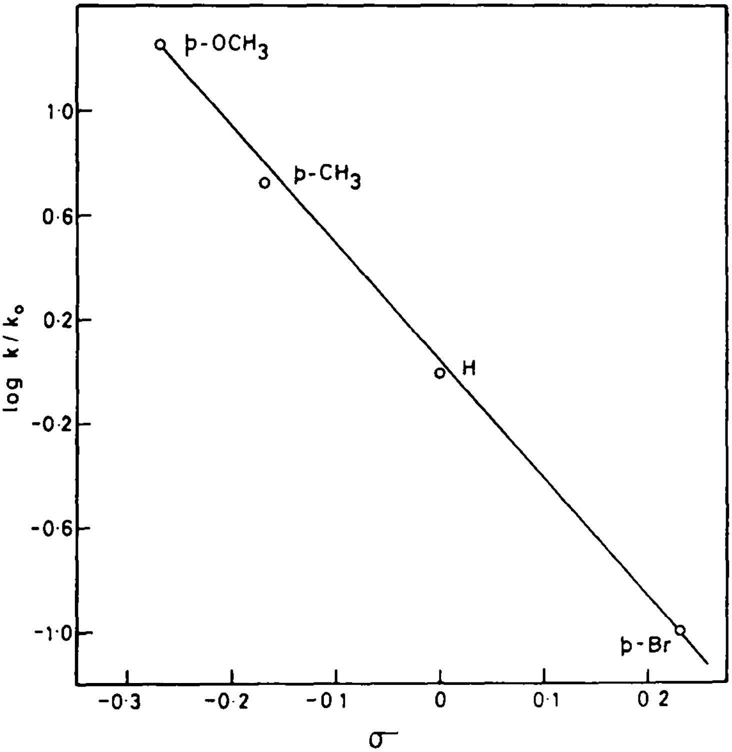

FIG. 7. Correlation of the second order rate data on the addition of substituted anilines to phenylisothiocyanate with the Hammett $\sigma$ constants of *p*-substituents.

The data clearly show that the rates are strongly dependent on the substituent on the aniline (Fig. 6). The log $k/k_0$ values show a good linear relation with the Hammett $\sigma$ constants of the *p*-substituents (Fig. 7), the rate increasing with the electron-donating power of the substituent. The least-square line is given by,

$$\log k/k_0 = 0{\cdot}017 - 4{\cdot}443\sigma \tag{5}$$

The correlation coefficient and standard deviation are 0·998 and 0·055 respectively. The basicity of anilines increases with the electron-donating power of the substituent.[15] The p$K_a$ of substituted anilines[15] is related to Hammett $\sigma$ constants of substituents by the equation,

$$\mathrm{p}K_a = 4{\cdot}45 - 2{\cdot}6\,(\sigma, \sigma^-) \tag{6}$$

The results clearly show the strong dependence of the addition reaction on the basicity or the nucleophilicity of amines. This is similar to the observations made in the case of nucleophilic substitution reactions where the rates are nearly proportional to the basicity of the nucleophilic reagents.[9–11]

The energies of activation of the addition reactions of substituted anilines with phenylisothiocyanates also do not show any dependence on the substituent constants,

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[15] H. C. Brown, D. H. McDaniel and O. Hafliger, in *Determination of Organic Structures by Physical Methods* (Edited by E. A. Braude and F. C. Nachod) Academic Press, New York (1955).

but vary in proportion to the corresponding entropies of activation (correlation coefficient of least-square line = 0·968).

## EXPERIMENTAL

The substituted phenylisothiocyanates were prepared by the oxidation of the corresponding ammonium dithiocarbamates.[16] Alkyl isothiocyanates were prepared by the reaction of the corresponding sodium dithiocarbamates with ethylchlorocarbonate.[17] All the alcohols and anilines were purified and dried before use. Triethylamine was dried over potassium hydroxide and fractionated before use. Dioxan was purified by refluxing with conc. hydrochloric acid and then with potassium hydroxide pellets till no aqueous layer separated. It was distilled over sodium pieces and stored over sodium wire.

Kinetics of the addition of alcohols to *p*-bromophenylisothiocyanate were studied in excess of alcohol (in the first order fashion) at 53·5° and 43·5° employing boiling acetone and carbon disulphide baths and a reaction vessel similar to that described by Lieber *et al.*[18] Since the reaction with t-butanol was extremely slow even at 53·5°, the kinetics were studied at 62° employing boiling methanol bath and at the boiling temp of t-butanol (79°). Even at these temps. the rates were too slow. Kinetics of the addition of aniline and substituted anilines to phenylisothiocyanates were studied at 40° and 30° using a thermostated water bath. The kinetics of addition of aniline to alkyl isothiocyanates were studied at 54·5° and 44·5°. During any one experiment the temp. did not vary more than ±0·3°.

The amount of the isothiocyanate in a reaction mixture was analysed either by the gravimetric method employing benzidine[19] or by the titrimetric procedure employing piperidine as the reagent.[8]

All the second-order rates were determined in dioxan medium in presence of triethylamine catalyst (0·01 M). It was necessary to add triethylamine in order to prevent the precipitation of thioureas.

*Thiourethanes.* The n-propanol adduct had a m.p. 46°. Found, C = 43·84; H = 4·618. Calc. C = 43·81; H = 4·381. The i-propanol adduct had a m.p. 109°. Found, C = 43·18, H = 4·92. Calc. C = 43·81, H = 4·381.

Near U.V. absorption spectra were recorded with a Hilger Uvispek, model H.700, spectrophotometer. The spectra reported in Fig. 2 were run in cyclohexane–isopropanol mixtures at ~25° and there was no reaction between the isothiocyanate and alcohol under these conditions.

*Acknowledgements*—The authors are thankful to Professor D. K. Banerjee and Professor M. R. A. Rao for their interest in the work.

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[16] F. B. Dains, R. Q. Brewester and C. P. Olander, *Organic Synthesis* Coll. Vol. I, p. 447, John Wiley, New York (1946).

[17] M. L. Moore and F. S. Crossley, *Organic Synthesis* Coll. Vol. III; p. 599. John Wiley, New York (1955).

[18] E. Lieber, C. N. R. Rao and T. S. Chao, *J. Amer. Chem. Soc.* **79**, 5962 (1957).

[19] D. W. Browne and G. H. Dyson, *J. Chem. Soc.* 3285 (1931).