Kinetics and Mechanism of Hydrolysis of *O*-Aryl *N*-Phenylthiocarbamates

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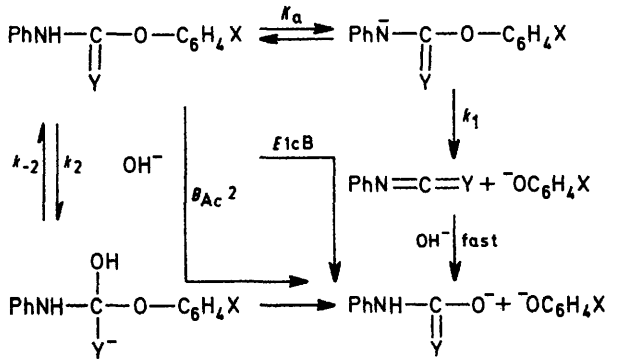
In kinetic studies of the hydrolysis of a series of *O*-aryl *N*-phenylthiocarbamates, evidence for the formation of phenyl isothiocyanate is a decisive argument for an *E*1cB mechanism. The high value of the Hammett parameter (ρ 3.0) and the positive value of the entropy of activation ($\Delta S^{\ddagger}$ + 10.8 cal mol^{-1} K^{-1}) are discussed as mechanistic criteria which can be used to establish the occurrence of an *E*1cB mechanism when the intermediate cannot be isolated.

ESTERS with a labile proton on the atom α to the carbonyl function can hydrolyse in alkali by an *E*1cB mechanism as well as *via* the $B_{Ac}2$ pathway involving a tetrahedral intermediate. This is illustrated by the hydrolysis of acetoacetates for which Pratt and Bruice [1] showed a changeover in mechanism which is sensitive to the nature of the leaving group: the lower the pK_a of its



SCHEME 1

conjugate acid, the better is its leaving ability. The unimolecular elimination mechanism has been discussed together with the $B_{Ac}2$ addition–elimination pathway for the hydrolysis of *N*-monosubstituted carbamates.[2-5] The main difference is the formation of an unstable isocyanate intermediate along the *E*1cB reaction pathway.

Though he gave no evidence for the isocyanate intermediate, Williams,[2] from an investigation of substituent effects on the leaving group, suggested an *E*1cB mechanism, previously put forward first by Dittert,[6] then by Bender and Homer.[7] On the other hand, Hegarty and Frost [3] gave indirect evidence for the formation of an isocyanate intermediate in the intramolecular cyclisation of *p*-nitrophenyl *N*-(*o*-aminophenyl)carbamate to *o*-phenyleneurea. After the rate-determining *E*1cB elimination, *o*-aminophenyl isocyanate is trapped by the amino-function. Likewise, these authors [5] showed that the cyclisation of phenyl *N*-(*o*-carbamoylphenyl)carbamate to 1,3-dihydroquinazoline-2,4-dione proceeds *via* trapping of the isocyanate intermediate by the amide.

Providing evidence for an *E*1cB mechanism for the hydrolysis of carbamates can be difficult; the conjunction of several arguments is necessary, for, separately, none is decisive. The only formal evidence that distinguishes between *E*1cB and $B_{Ac}2$ mechanisms is the isolation of the isocyanate intermediate. The instability of phenyl isocyanate in aqueous solutions precluding this, we set out to isolate phenyl isothiocyanate which is much more stable.[8,9] We present here the results of a study of the alkaline hydrolysis of a series of substituted

[1] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.
[2] A. Williams, *J.C.S. Perkin II*, 1972, 808.
[3] A. F. Hegarty and L. N. Frost, *J.C.S. Perkin II*, 1973, 1719.
[4] A. F. Hegarty and L. N. Frost, *J.C.S. Chem. Comm.*, 1972, 500.
[5] A. F. Hegarty, L. N. Frost, and J. H. Coy, *J. Org. Chem.*, 1974, **39**, 1089.
[6] L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, 1963, **52**, 852.
[7] M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975.
[8] K. Antos, J. Sura, V. Knoppova, and J. Prochazka, *Coll. Czech. Chem. Comm.*, 1973, **38**, 1609.
[9] V. Knoppova and M. Uher, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3852.

O-aryl *N*-phenylthiocarbamates which could hydrolyse *via* an *E*1cB mechanism.[10]

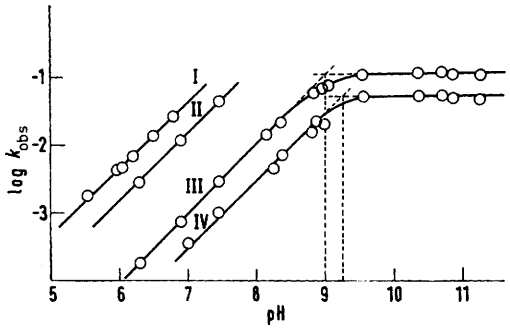
RESULTS AND DISCUSSION

The rates of hydrolysis of *O*-aryl *N*-phenylthiocarbamates have been investigated in water. Because of the low water solubility of the *N*-methyl analogues, measurements for these were carried out in 4 : 1 (v/v) water–ethanol. All reactions exhibited good first-order kinetics with respect to the substrate.

The products of hydrolysis were determined in all cases by comparing the u.v. spectrum obtained at the completion of a kinetic experiment with the spectrum of the expected products, run at the same concentration and under the same conditions. Thus, for the hydrolysis of *O*-4-acetylphenyl *N*-phenylthiocarbamate, the u.v. spectrum recorded at the end of reaction was identical with that of a mixture of phenyl isothiocyanate and 4-acetylphenol, whose concentrations were equal to the initial concentration of the ester. This shows unquestionably that the hydrolysis proceeds *via* an *E*1cB mechanism. Actual isolation of the product was also possible: further evidence came from the extraction of phenyl isothiocyanate obtained from macroscopic hydrolysis of *O*-3-acetylphenyl *N*-phenylthiocarbamate and its subsequent characterisation by i.r. and n.m.r. spectroscopy.

Thus having removed any doubt as to the reaction scheme for the hydrolysis of *O*-aryl *N*-phenylthiocarbamates, we set out to discuss the various arguments usually put forward for an *E*1cB mechanism when the isocyanate intermediate cannot be demonstrated.

The Figure shows a plot of the logarithms of the



Plot of the log of the observed rate constants *versus* pH for the hydrolysis of substituted *O*-phenyl *N*-phenylthiocarbamates $PhNHCSOC_6H_4X$ in water at 25° (μ 0.1, KCl): I, X = 4-Ac; II, X = 3-Ac; III, X = H; IV, X = 4-OMe

observed pseudo-first-order rate constants k_{obs} against pH for the hydrolysis of four thiocarbamates (X = H, 4-MeO, 4-Ac, and 3-Ac). These data are consistent with an E1cB mechanism (Scheme 1) with $k_{obs} = k_1K_a/(K_a + a_H)$. For X = H and 4-MeO, a plot of $(1/k_{obs})$ against 10^{-pH} leads to values (intercept/slope) of K_a of 9.09×10^{-10} mol l^{-1} (r 0.993) for $PhNHCSOPh$ and K_a 5.42×10^{-10} mol l^{-1} (r 0.997) for $PhNHCSOC_6H_4OMe$-4.

Substituent Effects.—The effect of the substituents X on the hydrolysis of compounds $PhNHCSOC_6H_4X$ is reflected upon the bimolecular rate constant $k_{OH} = k_1K_a/K_w$ (when $a_H \gg K_a$) by the linear free energy relationship $\log k_{OH} = (3.0 \pm 0.15)\ \sigma + 4.07$ (r 0.997). The k_{OH} values (Table 1) were derived for each compound

TABLE 1

Bimolecular rate constants k_{OH} for the hydrolysis of $PhNHCSOC_6H_4X$ at 25° (μ 0.1, KCl)

X	k_{OH}/l mol^{-1} s^{-1}	σ (σ⁻)
H	9.41 (±0.16) × 10^3	0
4-MeO	2.18 (±0.31) × 10^3	−0.268
4-Ac	4.14 (±0.04) × 10^5	0.502 (0.874)
3-Ac	1.57 (±0.02) × 10^5	0.376

from the observed rate constants k_{obs} over the pH range where the slope of $\log k_{obs}$ against pH is unity ($k_{OH} = k_{obs}10^{-pH}/K_w$).

The Hammett ρ value of 3.0 obtained for change of substituent on the leaving phenol group of *N*-monosubstituted thiocarbamates is in good agreement with those reported recently by Hegarty[3] (ρ 3.17) and Williams[2] (ρ 2.86) for oxygen analogues. This large substituent effect undoubtedly favours the elimination (*E*1cB) pathway. According to Williams, such a ρ value is much too high to be assigned to a $B_{Ac}2$ mechanism, for which a value near unity should be expected as observed for the alkaline hydrolysis of substituted phenyl acetates.[11]

In order to correlate the discussion of the magnitude of the ρ value with the reaction scheme, we investigated the effect of the substituent X on the hydrolysis of *NN*- disubstituted thiocarbamates $PhNMeCSOC_6H_4X$ (Table 2), for which the reaction mechanism is $B_{Ac}2$ (Scheme 2).

TABLE 2

Pseudo-first-order rate constants $10^4k_{obs}/s^{-1}$ for the hydrolysis of $PhMeCSOC_6H_4X$ in 4 : 1 (v/v) water–ethanol at 67.5° (μ 1.0, KCl)

[OH⁻]/M	X = 4-NO_2	X = 4-Ac	X = 4-Ac	X = 3-Ac	X = H	X = 4-MeO
1.002	22.2 [a]	11.13 [b]	10.94 [a]	6.72 [a]	2.74 [a]	2.03 [a]
0.748	17.6	8.35	8.35	5.37	2.23	1.57
0.502	11.9	5.71	5.56	3.45	1.50	1.12
0.242	6.3	3.00	2.92	1.57	0.77	0.67

[a] Measured from the disappearance of the substrate. [b] Measured from the formation of the substituted phenol.

The observed rate constant k_{obs} was proportional to the hydroxide ion concentration. The substituent effects on the bimolecular rate constant $k_{OH} = k_{obs}/[OH^-]$ are summarised in Table 3 and lead to the Hammett equation $\log k_{OH} = (1.05 \pm 0.06)\ \sigma - 3.52$ (r 0.994). This ρ value of *ca.* 1 obtained for substituent

[10] G. Sartore, M. Bergon, and J. P. Calmon, *Tetrahedron Letters*, 1974, 3133.

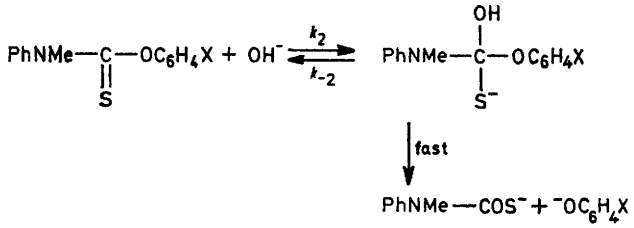
[11] E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801.

variation in the leaving group is quite consistent with hydroxide ion attack on the ester, followed by phenolate ion elimination.[11-14] This value, which is three times lower than that calculated for *N*-monosubstituted compounds (ρ 3.0) does correspond to that expected for a

TABLE 3

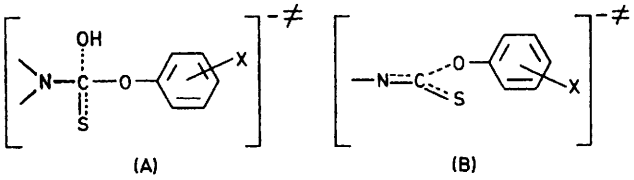
Bimolecular rate constants for the hydrolysis of PhNMeCSOC$_6$H$_4$X in 4 : 1 (v/v) water–ethanol at 67.5° (μ 1.0, KCl)

X	10^4k_{OH}/s^{-1}
4-NO_2	21.4 ± 0.7 (*r* 0.999)
4-Ac	10.8 ± 0.1 (*r* 0.999)
3-Ac	6.95 ± 0.37 (*r* 0.997)
H	2.66 ± 0.15 (*r* 0.997)
4-MeO	1.77 ± 0.01 (*r* 0.997)



SCHEME 2

$B_{Ac}2$ mechanism. Therefore, substituent effects are smaller for a $B_{Ac}2$ mechanism (where bond formation is occurring in the transition state A) than for an *E*1cB mechanism (where both bond formation and cleavage are involved in the transition state B).



Williams and Hegarty introduced Hammett σ⁻ values for substituents with high electron-withdrawing power, so as to obtain a better correlation for *N*-monosubstituted carbamates. We did not retain it for the 4-Ac substituent as the correlation was less satisfactory (*r* 0.966). In a similar case, for the hydrolysis of aryl *NN*-diphenylphosphorothiodiamidates, Williams and Douglas [15] correlated log k_{OH} with σ. According to these authors, the good Hammett relationships observed where σ (as opposed to σ⁻) is employed are in agreement with a small degree of P–OC$_6$H$_4$X cleavage in the transition state as opposed to advanced C–O cleavage in the analogous carbamate case, where the correlation with σ⁻ is explicable in terms of the marked phenolate ion character in the transition state. For the $B_{Ac}2$ mechanism, as C–OC$_6$H$_4$X bond cleavage is little advanced in the transition state, the Hammett correlation holds only for σ. Therefore, it seems that the higher polarisability of sulphur, relative to oxygen, enhances charge delocalisation from the anion, which could account for the smaller degree of C–OC$_6$H$_4$X bond cleavage in thiocarbamates than in carbamates.

The bimolecular rate constants also fitted a Brønsted relationship when the pK_a values of the departing phenols were employed: log $k_{OH} = -\beta pK_a + k'$.* Thus, β = 1.35 ± 0.07 (*r* 0.997) for PhNHCSOC$_6$H$_4$X and 0.47 ± 0.03 (*r* 0.994) for Ph(Me)CSOC$_6$H$_4$X. For the hydrolysis of PhNHCO$_2$C$_6$H$_4$X, Williams reported a Brønsted coefficient (1.34) identical with that for the series of the analogous thiocarbamates. According to him, such a Brønsted coefficient is too large to account for a mechanism where simple C–O bond breaking would occur, as in a $B_{Ac}2$ scheme (β = 0.25 for PhN(Me)CO$_2$C$_6$H$_4$X). As a matter of fact, a value greater than unity would be the result of a combination of an ionisation process (K_a), formation of the N–C bond, and fission of the C–O–Ar bond.

Entropy of Activation.—In addition to substituent effects, Arrhenius parameters can be used as a decisive argument to distinguish *E*1cB from $B_{Ac}2$ mechanisms: the former should show a considerably more positive entropy of activation than the latter. The effect of temperature on the rate constants was studied for the *E*1cB hydrolysis of phenyl *N*-phenylthiocarbamate (Table 4) and yielded an entropy of activation ΔS‡ + 10.8 cal mol^{-1} K^{-1}. A similar study for the $B_{Ac}2$ hydrolysis of the corresponding *N*-methyl analogue (Table 5) led to a ΔS‡ value of −23.8 cal mol^{-1} K^{-1}. The positive entropy of activation determined for PhNHCSOPh is quite consistent with an *E*1cB mechanism where the

TABLE 4

Pseudo-first-order rate constants for the hydrolysis of PhNHCSOPh in phosphate buffer (pH 6.93) at various temperatures (μ 0.1, KCl)

t/°C	20.8	25	31.8	40.7
10^4k_{obs}/s^{-1}	4.56	7.95	21.9	68.3

TABLE 5

Rate constants k_{obs} and k_{OH} for the hydrolysis of PhNMeCSOPh in 4 : 1 (v/v) water–ethanol at various temperatures (μ 1.0, KCl)

t/°C	50	59.4	67.5	78.6
[OH⁻]/M	10^5k_{obs}/s^{-1}	10^4k_{obs}/s^{-1}	10^4k_{obs}/s^{-1}	10^4k_{obs}/s^{-1}
1.002	6.91	1.38	2.74	6.38
0.748	5.25	1.03	2.23	5.37
0.502	3.52	0.691	1.50	3.45
0.248	1.86	0.345	0.77	1.96
k_{OH}/	0.675	1.38	2.66	6.61
l mol^{-1} s^{-1}	±0.04 (*r* 0.999)	±0.01 (*r* 0.999)	±0.15 (*r* 0.997)	±0.25 (*r* 0.998)

* The pK_a values of the leaving groups were calculated using the relationship pK_a = 9.92 + 2.23 σ.[16]

[12] A. Williams and R. A. Naylor, *J. Chem. Soc.* (*B*), 1971, 1967.
[13] J. J. Ryan and A. A. Humphray, *J. Chem. Soc.* (*B*), 1966, 842.
[14] T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, 1960, **82**, 3067.
[15] A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1973, 318.
[16] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, 388.

rate-determining step is elimination of phenoxide ion from the conjugate base of the substrate to give the isothiocyanate intermediate. Christenson [17] reported similar data for the *E*lcB hydrolysis of phenyl *N*-phenylcarbamate ($\Delta S^{\ddagger}$ + 5 cal mol^{-1}, K^{-1}), as well as Branstad and his co-workers [18] for that of PhNHCO(SPh) ($\Delta S^{\ddagger}$ + 21.1 cal mol^{-1} K^{-1}).

It is noteworthy that a positive entropy of activation allows us to rule out the occurrence of a $B_{Ac}2$ mechanism for which a negative entropy should be measured, as was observed for the hydrolysis of PhN(Me)CSOPh ($\Delta S^{\ddagger}$ − 23.8 cal mol^{-1} K^{-1}).

Thus, in summary, the successful isolation of phenyl isothiocyanate removes any ambiguity as to the nature of the mechanism of hydrolysis of *O*-phenyl *N*-phenylthiocarbamates and allows a discussion of the mechanistic value of some parameters such as Hammett's ρ, Brønsted's β, and the entropy of activation.

EXPERIMENTAL

Substrates —Substituted phenyl chlorothioformates. To a stirred solution of thiophosgene in chloroform was added dropwise an alkaline solution (1M < NaOH < 2M) of substituted phenol. The mixture was kept cold with ice for 1 h. The organic phase was then extracted, washed twice with water, and dried over $CaCl_2$. After evaporation of the solvent, chlorothioformate was obtained by distillation at reduced pressure.

O-*Aryl* N-*phenyl*- and N-*methyl*-N-*phenyl-thiocarbamates.* $PhNRCSOC_6H_4X$. Substituted *O*-phenyl *N*-phenyl- and *N*-methyl-*N*-phenyl-thiocarbamates, with the exception of the *p*-nitrophenyl ester, were prepared by the method of Rivier [19] from chlorothioformates and aniline or *N*-methylaniline. To a stirred solution of phenyl chlorothioformate in acetone was added aniline over 10 min and the mixture was refluxed for 5—10 min. The carbamate, which precipitated in cold water, was filtered off and recrystallised from ethanol; m.p. 158° (decomp.) (lit.,[19] 153—155°). Similarly prepared were: R = H, X = 3-Ac, m.p. 138—141° (from acetone); R = H, X = 4-Ac, m.p. 125° (decomp.) (from acetone); R = Me, X = H, m.p. 103° (from water–acetone) (lit.,[19] 104°); R = Me, X = 3-Ac, m.p. 136—137° (from acetone); R = Me, X = 4-Ac, m.p. 108° (from acetone). To a stirred solution of *p*-methoxyphenyl chlorothioformate in carbon tetrachloride, kept at 0°, was added the amine. The mixture was then stirred at room temperature for 24 h. The white precipitate of anilinium or *N*-methylanilinium chloride was filtered off and the filtrate evaporated to dryness to give the carbamate: R = H, X = 4-MeO, m.p. 120—121° (from benzene) (lit.,[20] 119—120°); R = Me, X = 4-MeO, m.p. 97—99° (from ethanol) (lit.,[21] 99—100°).

O-p-*Nitrophenyl* N-*methyl*-N-*phenylthiocarbamate.* To a stirred solution of thiophosgene in chloroform, kept at 0°, was added *N*-methylaniline within 1 h. The mixture was then stirred at room temperature for 24 h. Then, thiocarbamoyl chloride was added to *p*-nitrophenol dissolved in alkaline 1 : 1 (v/v) water–acetone and the reactants were refluxed for 20—30 min. After cooling, the precipitated carbamate was recrystallised from ethanol; m.p. 130—133° (lit.,[21] 130—132°).

The structures assigned to the thiocarbamates were confirmed by n.m.r. spectroscopy.

Apparatus.—A Unicam model SP 1800 recording spectrophotometer fitted with an SP 1805 programme controller and a thermostatted multiple cell compartment was used for all spectroscopic measurements. The pH measurements were carried out using a Beckman research pH meter.

Kinetic Method.—The kinetics of hydrolysis of *N*-monosubstituted thiocarbamates were investigated in aqueous solutions at 25° whereas those of *NN*-disubstituted thiocarbamates were studied in 4 : 1 (v/v) water–ethanol containing sodium hydroxide at 67.5°. All reactions were followed spectrophotometrically at appropriate wavelengths in the u.v. region: the changes in optical density corresponding to the disappearance of the substrate and the appearance of the products, phenol or phenyl isothiocyanate, were recorded. Initial repetitive scans of the u.v. region established that these reactions had tight isosbestic points, indicating the absence of intermediates.

The absorbance *versus* time plots were analysed in all cases to give the pseudo-first-order rate constants graphically, either by the method of Guggenheim, or using the experimental infinity value.

The entropies of activation $\Delta S^{\ddagger}$ were obtained from the equation $\Delta S^{\ddagger}$ 2.303 R (log k_{obs} − log T − log eK/h) + E_0/T and regression lines from a weighted least squares program written for the Olivetti–Underwood Programma 102.

Characterisation of Phenyl Isothiocyanate.—Comparison of u.v. spectra. The u.v. spectrum recorded at the completion of the hydrolysis of *O*-*p*-acetylphenyl *N*-phenylthiocarbamate at pH 8.27 was identical with the spectrum of an authentic sample of the products (*viz.* phenyl isothiocyanate and *p*-acetylphenol) run at the same concentration and under the same conditions.

Extraction and spectroscopic identification. The experiment could also be repeated on a preparative scale. Thus, to a solution of *O*-*m*-acetylphenyl *N*-phenylthiocarbamate (135.5 mg, 0.01M) in dioxan (50 ml) was added an aqueous sodium borate solution (100 ml). This 2 : 1 (v/v) water–dioxan mixture of pH 11.85 (μ 1.0 KCl) was stirred for 45 min at 25°. The aqueous phase was then extracted with portions of carbon tetrachloride (6 × 15 ml). The extracts were washed with $NaHCO_3$ so as to remove *m*-acetylphenol. Then they were dried over $CaCl_2$ and the solvent was evaporated to dryness.

The i.r. and n.m.r. spectra of the residue obtained were identical with those of an authentic sample of phenyl isothiocyanate and exhibited the characteristic bands of the N=C=S group (ν_{as} 2 089, ν_s 927 cm^{-1}) [22] and the characteristic signal of the phenyl group (δ 7.23).

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