The *E*1cB Mechanism for Thiocarbamate Ester Hydrolysis: Equilibrium and Kinetic Studies

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The alkaline hydrolyses of a series of *S*-aryl thiocarbamate esters have been measured and the mechanism confirmed to be dissociative. Equilibrium constants for the synthesis of thiocarbamates from thiol and isocyanic acid have been obtained for aqueous media using both kinetic and analytical techniques. Hammett and Brønsted parameters for the equilibrium reaction indicate that there is less positive effective charge on the sulphur in the thiocarbamate compared with that on the oxygen in the oxygen analogue. Theoretical arguments are advanced to show that the dissociative reactions of simple carbamate anions involve a planar geometry of the participating atoms.

The alkaline hydrolysis of carbamate esters has been shown conclusively to involve a dissociative step followed by decomposition of the intermediate isocyanate to amine and carbon dioxide.[1] The detailed electronic nature of this reaction has been probed by the use of structure–reactivity relationships with regard to the ether oxygen in the oxygen esters.[1a] Electronic probing at a fundamental level has also been carried out on the analogous thioncarbamate equilibrium with isocyanate and phenol[2] and this indicates a more positive effective charge on the thione ether oxygen compared with that in the oxygen analogue [equations (1) and (2)].

$$\overset{(+0.81)}{\text{RNH–CO–O–R'}} \xrightarrow{HO^-} \text{RNCO} + \text{R'O}^- \qquad (1)$$

$$\overset{(+1.44)}{\text{RNH–CS–O–R'}} \xrightarrow{HO^-} \text{RNCS} + \text{R'O}^- \qquad (2)$$

Previous studies have indicated that thiocarbamates hydrolyse in alkali through a path involving prior dissociation to isocyanate.[1d,e] The relative ease with which the reaction [equation (3)] between thiol and isocyanate ion may be

$$\text{RNH–CO–S–R'} \xrightarrow{HO^-} \text{RNCO} + \text{R'S}^- \qquad (3)$$

measured spectrophotometrically using aqueous media makes this a very attractive system to study. Hupe and Jencks[3] indicated that much less positive effective charge (+0.38) is developed on the sulphur in thiolacetates (measured against the standard change in charge in the ionisation of thiols) compared with that (+0.7) seen in the ether oxygen in analogous oxygen acetate esters.[4] The present system is ideal for a similar comparison in the series where the ether oxygen of the carbamate is replaced by a sulphur. We discuss also the stereochemistry of the equilibrium reaction between thiocarbamate and product isocyanate and thiol.

Experimental

Materials.—Thiols were obtained commercially, except for 3-nitrothiophenol which was prepared by reduction of the disulphide with triphenylphosphine.* A mixture of triphenylphosphine (14.7 g), methanol (7 ml), and acetic acid (3 ml) was kept at 70 °C for 30 min under an atmosphere of nitrogen. The mixture was cooled to room temperature, bis-(3-nitrophenyl) disulphide (7.1 g) added, and the mixture stirred for 30 min before maintaining the temperature at 50 °C for 3 h. The mixture was cooled and basified with NaOH solution (8 g in 35 ml water). The filtered solution was acidified, extracted with dichloromethane (2 × 30 ml), and the organic layer dried with $MgSO_4$. The thiol was obtained by evaporation and used directly. Phenyl isocyanate was redistilled before use. *N*-Phenylthiocarbamate esters were synthesised by warming the appropriate thiol with phenyl isocyanate for 15 min. *S*-Phenyl thiocarbamate was prepared as in a previous study[1a] from KNCO and thiophenol.

S-(4-Methylphenyl) thiocarbamate was prepared by adding dropwise a solution of 4-methylthiophenol (5 g) in tetrahydrofuran (4 ml) and acetic acid (4 ml) to a stirred solution of KNCO (3.2 g) in water (100 ml). The addition took 15 min and the mixture was stirred for a further 45 min and the product recovered by filtration. The resultant ester was recrystallised twice from tetrahydrofuran–light petroleum. *S*-(4-Chlorophenyl) thiocarbamate was prepared by the above method and *S*-(4-methoxyphenyl) thiocarbamate was prepared by addition of acetic acid to a mixture of the thiophenol and KNCO in water. The other *S*-aryl thiocarbamates were obtained by the method illustrated below for *S*-(4-bromophenyl) thiocarbamate. Chlorosulphonyl isocyanate (1.4 g) was added to 4-bromothiophenol (1 g) and the mixture agitated. After 20 min the mixture was treated cautiously with water (7 ml) and kept for a further 30 min after which the product was isolated by filtration. The ester was recrystallised from toluene.

Analytical and physical data for the esters are presented in Table 1. I.r. and n.m.r. data are consistent with the proposed structures of the thiocarbamate esters.

Buffer components were from analytical grade material and water, used throughout the investigation, was redistilled twice from glass. Acetonitrile was purified by the method of Lewis and Smyth[5] followed by distillation from a small quantity of calcium hydride.

Methods.—Kinetic measurements. Rate measurements were carried out spectrophotometrically using either a GCA-McPherson 707-K double-beam instrument or a Pye–Unicam SP-800 machine with cell compartments thermostatted to

* We are grateful to Dr. R. S. Davidson (University of Kent) for this recipe.

Table 1. Analytical and physical data for thiocarbamate substrates[a]

Substrate	M.p. (°C)	Found (%) C	H	N	Formula	Calculated (%) C	H	N
Parent thiocarbamates								
S-4-Methylphenyl[g]	171—172[d] (171)[b,d]	57.5	5.2	8.2	C_8H_9NOS	57.5	5.4	8.4
S-4-Methoxyphenyl[h]	122—123 (131)[b]	52.4	4.9	8.1	$C_8H_9NO_2S$	52.5	4.9	7.7
S-4-Chlorophenyl[k]	(dec.)[c] (176)[b,d]	44.7	2.8	7.4	C_7H_6ClNOS	44.8	3.2	7.5
S-4-Bromophenyl[m]	(dec.)[c] (184)[b,d]	36.1	2.5	5.9	C_7H_6BrNOS	36.2	2.6	6.0
S-3-Nitrophenyl	124—127 (124)[b]	42.5	2.9	14.1	$C_7H_6N_2O_3S$	42.4	3.0	14.1
S-4-Nitrophenyl[n]	157—160 (157)[b,d]	42.5	2.8	14.0	$C_7H_6N_2O_3S$	42.4	3.0	14.1
N-Phenyl thiocarbamates								
S-4-Chlorophenyl	152.5—155	59.2	3.7	5.4	$C_{13}H_{10}ClNO_3S$	59.2	3.8	5.3
S-4-Methylphenyl	130—132 (127)[e]							
S-2-Methylphenyl	148—150.5	69.3	5.6	5.8	$C_{14}H_{13}NOS$	69.1	5.4	5.8
S-3-Chlorophenyl	122.5—123.5	59.3	3.7	5.4	$C_{13}H_{10}ClNO_3S$	59.2	3.8	5.3
S-3-Nitrophenyl	111—113	56.8	3.7	10.2	$C_{13}H_{10}N_2O_3S$	56.9	3.9	10.2
S-Phenyl	122—124 (122—122.5)[f]							

[a] Analyses by Mr. A. J. Fassam of the University of Kent or by Chemanalytics Inc. (Arizona). [b] R. Riemschneider, F. Wojahn, and G. Orlick, *J. Am. Chem. Soc.*, 1951, **73**, 5905. [c] Decomposition obscured the m.p. in our samples. [d] Melts with decomposition. [e] H. Gilman and W. B. King, *J. Am. Chem. Soc.*, 1925, **47**, 1141. [f] H. Rivier, *Bull. Soc. Chim. Fr.*, 1907, 733. [g] Found: S, 19.4. Calc.: 19.2%. [h] Found: S, 17.5. Calc.: 17.5%. [k] Found: S, 17.3. Calc.: 17.1%. [m] Found: S, 14.2. Calc.: 13.8%. [n] Found: S, 16.1. Calc.: 16.2%.

25 ± 05 °C. Substrate (10—50 μl of stock solution in acetonitrile) was added on the flattened tip of a glass stirring rod to 2.5 ml of the appropriate degassed medium, equilibrated to 25 °C in a 1 cm path length silica cell. The reaction chamber was flushed with nitrogen to prevent disulphide formation which interfered with the kinetics. Radiometer PHM 64 and PHM 26 pH-meters were used (calibrated to ±0.01 pH units) for pH measurements which were carried out on the reaction solutions at the end of a kinetic run. The optimum wavelengths for the kinetic studies were determined by repetitive scanning of the spectrum of a test reaction.

Kinetics of the hydrolyses of the *N*-phenylthiocarbamates were studied by a novel scavenging technique which depends on the rapid reaction of the released thiol [equation (4)] with a

$$\mathrm{PhNH{-}CO{-}S{-}R} \xrightarrow{\text{slow}} \mathrm{PhNCO} + \mathrm{R{-}S^-} \xrightarrow[\text{fast}]{\mathrm{R'SSR'}} \mathrm{R{-}S{-}S{-}R'} + \mathrm{R'{-}S^-} \quad (4)$$

chromogenic disulphide such as Ellman's reagent [5,5'-dithiobis-(2-nitrobenzoic acid), DTNB] or 2,2'-dipyridyl disulphide (DPDS). In this way rates may be measured at 412 nm (DTNB) or 343 nm (DPDS) independently of the change in absorbance of the thiocarbamate. The reaction medium contained ethylenediaminetetra-acetic acid (1.25×10^{-5}M), a suitable concentration of acetonitrile, and buffer components to yield the appropriate ionic strength. In addition, DTNB or DPDS were present at concentrations between 0.05 and 0.4mM. The thiolytic reaction with scavenger disulphides is known to be rapid.[6a] That the scavengers are trapping the thiol in a fast step is indicated by the independence of the rate constant on the concentration and nature of the trapping species. The rate constants measured in the presence of the trapping agent for *S*-phenyl *N*-phenylthiocarbamate are $2.63 \pm 0.35 \times 10^{-3}$ (DTNB) and $3.06 \pm 0.26 \times 10^{-3}$ s^{-1} (DPDS) at pH 5.75 in phosphate buffer for trapping reagent concentrations of 0.069—0.414 mM respectively.

Molecular orbital calculations. Calculations of energies were made using a CNDO/2 program[6b] with a basis set including 3*d* orbitals on sulphur. The geometries of the ions were obtained from crystallographic data[6c] and where unknown were calculated by the application of additivity rules. Computations were carried out on the University of London CDC computer *via* the University of Kent Computer Centre.

Results

Synthesis of Thiocarbamates.—We assume equations (5a) and (5b) are correct for the analysis of kinetics using KNCO-

$$\begin{array}{ccc} \mathrm{Ar{-}S{-}CONH_2} \underset{k_1}{\overset{k_{OH}[OH^-]}{\rightleftharpoons}} \mathrm{Ar{-}S^-} & + & \mathrm{HNCO} \\ \mathrm{H^+}\downarrow\uparrow & & \mathrm{-H^+}\downarrow\uparrow \\ \mathrm{Ar{-}SH} & & \mathrm{NCO^-} \\ (K^{\mathrm{ArSH}}) & & (K^{\mathrm{HNCO}}) \end{array} \quad (5a)$$

$$K_1 = [\mathrm{ArS^-}][\mathrm{HNCO}]/[\mathrm{ArSCONH_2}][\mathrm{OH^-}] \quad (5b)$$

containing buffers. Addition of KNCO (up to 1.6×10^{-2}M) is sufficient to cause the synthesis of thiocarbamates to become significant against degradation at pH values between 5 and 7. The observed rate constant will thus be as in equation (6) where

$$K_{obs} = k_{OH}[OH^-] + k_1[HNCO]f(\mathrm{Ar\text{-}S^-}) \quad (6)$$

$f(\mathrm{Ar\text{-}S^-})$ is the fraction of total thiol present as the anion. Substitution into equation (6) using the appropriate ionisation constants yields an expression [equation (7)] relating k_{obs}

$$k_{obs} = k_{OH}[OH^-] + k_1[NCO^-][H^+]/K^{HNCO}(1 + [H^+]/K^{ArSH}) \quad (7)$$

linearly with NCO^-. The value of K^{HNCO} is taken to be 3.29 at 25 °C and 1M ionic strength.[7] A typical plot of k_{obs} *versus* [KNCO] is given in Figure 1 from which k_1 may be calculated. At the pH values employed in this study the decomposition of cyanate is of negligible significance. For example, under the conditions reported in Figure 1 the rate constant for cyanate decomposition is *ca.* 1% of the total rate constant at zero added KNCO.

The approach to equilibrium was usually followed by addition of thiocarbamate substrate and to check the system we monitored the reaction for the addition of thiols to KNCO buffers. If equation (6) is correct we should obtain rate constants (at the KNCO concentration in question) similar to

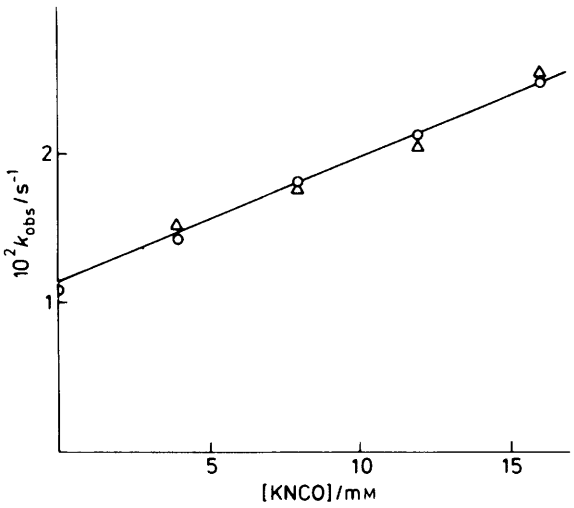


Figure 1. Rate constants for the decomposition of *S*-(4-bromophenyl) thiocarbamate (○) in buffers at pH 6.07 containing increasing amounts of KNCO at 25 °C and 1M ionic strength (made up with KCl). The line is theoretical calculated from data in Tables 2 and 3. Rate constants for the reaction of 4-bromophenol (△) with the cyanate buffers under the same conditions are shown

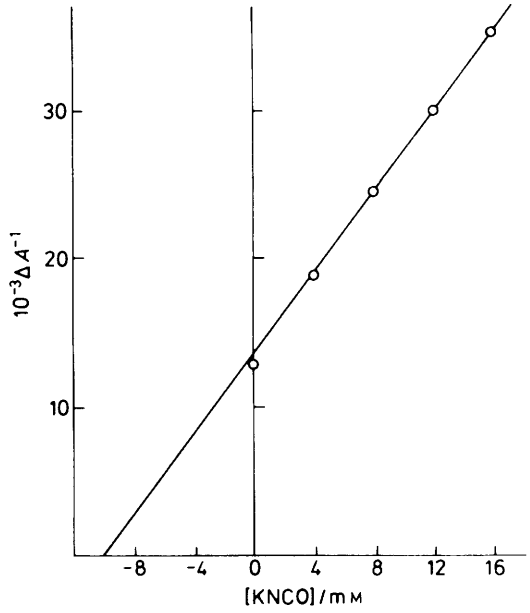


Figure 2. Dependence of the change in absorbance (ΔA) on the added KNCO concentration for the approach to equilibrium of *S*-(4-bromophenyl) thiocarbamate in buffers at pH 6.07. The line is calculated from data in Table 2 and from equation (10)

those for the degradation. Figure 1 reveals that the 'synthetic' rate constants for 4-bromothiophenol fit the 'degradative' line consistent with the proposed kinetic scheme.

Determination of Equilibrium Constant (K_1).—The equilibrium constant (K_1) may be determined analytically from the thiol concentration as measured spectroscopically after equilibrium has been reached. The method can only be applied to the parent carbamates because the isocyanic acid is stabilised against hydrolysis by ionisation; *N*-substituted carbamates yield isocyanates which hydrolyse quite rapidly.[7] The data come from the traces used to measure k_1 where a constant concentration of thiocarbamate is equilibrated in buffers containing increasing amounts of KNCO. Equation (8) relates

$$\Delta A/(\Delta A_{max.} - \Delta A) = ([ArS^-] + [ArSH])/[ArSCONH_2] \quad (8)$$

the change in absorbance at the given wavelength with product formation at equilibrium. ΔA is the change in absorbance to equilibrium in a given KNCO concentration and $\Delta A_{max.}$ is the absorbance change (at zero [KNCO]) for complete release of thiol equivalent to total hydrolysis. Equation (8) can be rearranged using the ionisation of ArSH and HNCO to give equations (9) and (10); a plot of $1/\Delta A$ *versus* $[NCO^-]$ is linear

$$\Delta A/(\Delta A_{max.} - \Delta A) = [ArS^-](1 + [H^+]/K^{ArSH})/[ArSCONH_2] \quad (9)$$

$$(1/\Delta A)(K_1[OH^-]/\Delta A_{max.}) - K_1[OH^-] = [NCO^-][H^+]/K^{HNCO}(1 + [H^+]/K^{ArSH}) \quad (10)$$

and is illustrated in Figure 2 for the equilibrium between *S*-(4-bromophenyl) thiocarbamate and its degradation products. The value of K_1 is obtained from the intercept at $1/\Delta A = 0$ and is given by equation (11).

$$K_1 = -[\text{intercept}][H^+]^2/K_w K^{HNCO}(1 + [H^+]/K^{ArSH}) \quad (11)$$

Determinations for the *S*-nitrophenyl thiocarbamates were carried out at pH 5.5 (for the 3-substituent) and 4.9 (for the 4-substituent). These low pH values, not used for the other esters, were necessary to keep the reaction at a measureable rate. The cyanic acid decomposition was raised to an appreciable level, however, resulting in a slowly increasing value of ΔA after the equilibrium had been reached. The slow change in ΔA was approximately linear and only a small proportion of the total change; a rough allowance was made by extrapolating to zero time. The equilibrium constants measured analytically were slightly different from those obtained by dividing k_{OH} by k_1 but not by more than could be accounted for by the experimental error (see Table 2). The largest difference is in the values for the 4-nitrophenyl ester where the cyanate hydrolysis becomes significant.

The values of k_1 and K_1 are recorded in Table 2 together with the conditions. These data conform to excellent linear Hammett equations [equations (12) and (13).]. The 4-nitro datum is

$$\log k_1 = (-0.89 \pm 0.16)\sigma + 3.26 \pm 0.06 \ (r\ 0.944) \quad (12)$$

$$\log K_1 = (2.63 \pm 0.1)\sigma + 2.07 \pm 0.06 \ (r\ 0.989) \quad (13)$$

omitted from these correlations as it is uncertain what value of σ is to be used. The equation for K_1 includes both analytically and kinetically determined values.

Alkaline Hydrolysis of Thiocarbamates.—Plots of log k_{obs} *versus* pH at zero added KNCO were linear with slopes close to unity. The rate constant for hydrolysis of *S*-phenyl *N*-phenylthiocarbamate was independent of free added aniline concentration up to 0.03M at pH 4.80 and 0.2M ionic strength. The values of k_{OH} for the *S*-aryl thiocarbamates obey an excellent Hammett equation (14) omitting the value for the 4-nitro

$$\log k_{OH} = (1.7 \pm 0.03)\sigma + 5.39 \pm 0.02 \ (r\ 0.999) \quad (14)$$

substituent which could be fitted assuming a σ value of 1.15. The Hammett equation for the *N*-phenylthiocarbamates omitting the 2-methylphenyl and ethoxycarbonylmethyl esters has a slightly higher ρ value (2.36 ± 0.13) for a smaller spread of

Table 2. Synthesis of *S*-aryl thiocarbamates in aqueous solution at 25 °C, 1.0M ionic strength[a,d]

Substituent	10^3k_1/l mol^{-1} s^{-1}	K_1	N^b	pH	k_{OH}/k_1[c]
Parent	1.5 ± 0.1	120 ± 12	10	6.4	160 ± 11
4-Methyl	1.8 ± 0.15	43 ± 8	10	6.9	72 ± 6
4-Methoxy	4.1 ± 0.4	16 ± 2	14	6.9	20 ± 2
4-Chloro	1.6 ± 0.1	280 ± 20	14	6.3	360 ± 22
4-Bromo	1.1 ± 0.05	580 ± 50	12	6.1	760 ± 35
3-Nitro	0.38 ± 0.05	$7.6 \pm 2 \times 10^3$	26	5.5	$1.1 \pm 0.14 \times 10^4$
4-Nitro	0.18 ± 0.035	$9.5 \pm 1.5 \times 10^4$	16	4.9	$1.7 \pm 0.33 \times 10^5$

[a] Thiol acidities and monitoring wavelengths given in Table 3. [b] Number of data points including duplicates and those from both degradation and synthetic kinetics (see text). [c] Values of k_{OH} used here are taken from Table 3. [d] Phosphate buffers employed at 0.005M concentration. No buffer concentration effects were observed up to 0.2M.

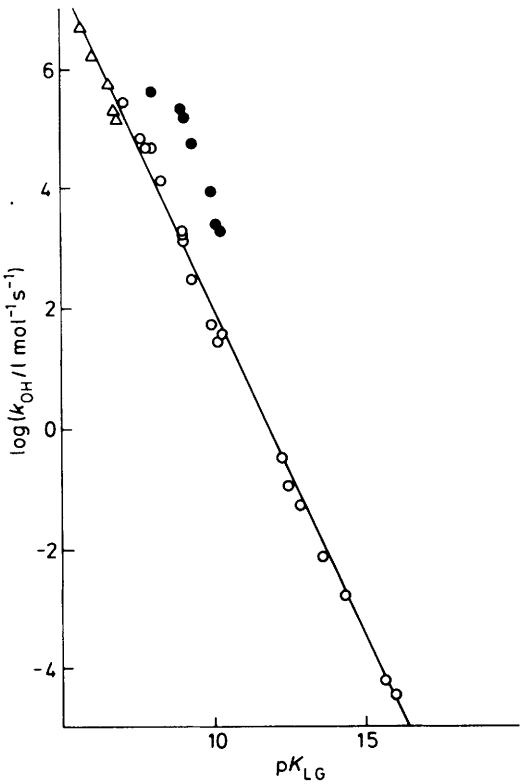


Figure 3. Brønsted-type dependence for the alkaline hydrolysis of *N*-phenylcarbamates. Data for thiocarbamates (△) are from this study, carbamates (○) from ref. 1*a*, and *N*-phenylthiocarbamates (●) from ref. 2

points. The Brønsted equation, illustrated in Figure 3, enables us to utilise all the data points for the *N*-phenylcarbamates and the sensitivity of the rate constant to the pK of the thiol leaving group is $\beta_L - 1.02 \pm 0.13$.

Discussion

This work confirms the conclusions of previous workers[1d,e] that alkaline degradation of thiocarbamates involves prior dissociation to form isocyanate and thiol (*E*1cB mechanism) rather than direct attack of alkali on the carbonyl function ($B_{Ac}2$ mechanism). The rate constant for the alkaline hydrolysis of the parent aryl thiocarbamate esters (k_{OH}) fits an excellent Hammett equation with a large positive slope; the 4-nitro substituent only fits the correlation when a σ^- value (in this case 1.15) is chosen. The large slope and σ^- dependence is consistent with a substantial negative charge on the sulphur in the transition-state of the rate-limiting step. The very large Hammett coefficient also indicates an *E*1cB mechanism for the *N*-phenyl series. Further evidence for the formation of isocyanate ion in the thiocarbamate degradation includes the *acceleration* of the rate for release of thiophenol by added KNCO. This and the identity of the 'synthetic' and 'degradative' rate constants at a give KNCO concentration (Figure 1) would not obtain if a *B*Ac2 process were involved.

The agreement between K_1 determined kinetically (k_{OH}/k_1) and from spectroscopic analysis (Table 2) is also consistent with the proposed mechanism. The sensitivity to Hammett's σ of K_1 determined analytically (2.63) is very close to that derived from the sensitivities of k_{OH} and k_1 (1.7 + 0.89 = 2.59) providing further confirmation of the *E*1cB mechanism.

Although an *E*2 mechanism for the isocyanate formation is not excluded by these results (thiolate ion is released concerted with hydroxide attack on hydrogen of the neutral carbamate) it is not likely in view of previous work.[1,2] The absence of general base catalysis is certainly consistent with the *E*1cB pathway.

Figure 3 indicates that the lability of thiocarbamates to hydroxide ion (k_{OH}) is similar to that of the oxygen esters for leaving groups of similar acidity. It is well known, however, that thiolate anions are weaker nucleofuges than oxyanions of the same basicity.[8a–c] The similarity of the k_{OH} values must therefore come from a compensating effect where the acidity of the NH of the thiocarbamate exceeds that of the oxygen analogue leading to a higher concentration of the conjugate base of the former at a given pH. We are not in a position to measure the pK of the carbamates directly but it is certainly well established that the stability of an anion adjacent to divalent sulphur is markedly increased over that of the oxygen analogue.[8d–f]

The effective charge distribution in the reaction between isocyanic acid and thiolate ion may be deduced against the ionisation of thiophenols in water (ρ 1.81)[9] as the standardising equilibrium. The effective charges are represented in Figure 4 in comparison with the analogous reaction of phenolate ions with isocyanic acid. It is not likely that the substituent change in the aryl ring would be transmitted to the same extent in the sulphur as in the oxygen case so that we cannot assume that the change in charge at sulphur on ionisation of the thiocarbamate is the same as for the carbamate; we cannot therefore measure the change in charge on sulphur for the simple elimination step. It is interesting, however, that the thiocarbamate ester has significantly less positive charge on the sulphur relative to that found on oxygen in the carbamate.[1a] This may be due to poor overlap between the 3*p* orbital on the sulphur and the 2*p* orbital on the carbon relative to the overlap in the oxygen case,[10] disfavouring structures of the type (**I**) which are possible for oxygen (**II**). A similar explanation has been advanced for the

Table 3. Degradation of thiocarbamate esters in aqueous solution at 25 °C, 1.0M ionic strength[h]

Substrate	pK^{RSH}[a]	$10^5 k_{OH}$/l mol^{-1} s^{-1}	N[b]	ΔpH[c,h]	λ/nm[d]
S-Aryl thiocarbamates					
Parent	6.62	2.4 ± 0.1 (2.3)[e]	8	5.5—7.0	290
4-Methyl	6.82	1.3 ± 0.1	8	6.5—8.0	275
4-Methoxy	6.78	0.80 ± 0.005	12	6.0—8.0	268
4-Chloro	6.14	5.7 ± 0.3	10	6.0—7.5	272
4-Bromo	6.02	8.4 ± 0.5	8	5.5—6.5	280
3-Nitro	5.24	40 ± 3	10	5.5—7.0	280
4-Nitro	4.72	310 ± 25	5	4.0—5.5	410
S-Aryl *N*-phenylthiocarbamates[g]					
3-Chloro	5.78	49 ± 0.04	2	5.84—6.26	
4-Chloro	6.14	16 ± 0.12	3	5.84—6.26	
Parent	6.62	5.1 ± 0.03	3	5.84—6.26	
4-Methyl	6.82	2.2 ± 0.02	3	5.84—6.26	
2-Methyl	7.0	1.4 ± 0.05	3	5.84—6.26	

[a] Acidities from ref. 9 at 25 °C. [b] Number of data points including duplicates. [c] Range of pH employed. [d] Wavelengths used to monitor the reaction. [e] Value from ref. 1*a*. [f] M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, and L. T. Ditsch, *J. Am. Chem. Soc.*, 1960, **82**, 4899. [g] Rate constants measured by the thiol trapping method. [h] Phosphate buffers were employed at 0.005M; no corrections were necessary to allow for buffer effects as none were observed up to 0.2M buffer concentration.

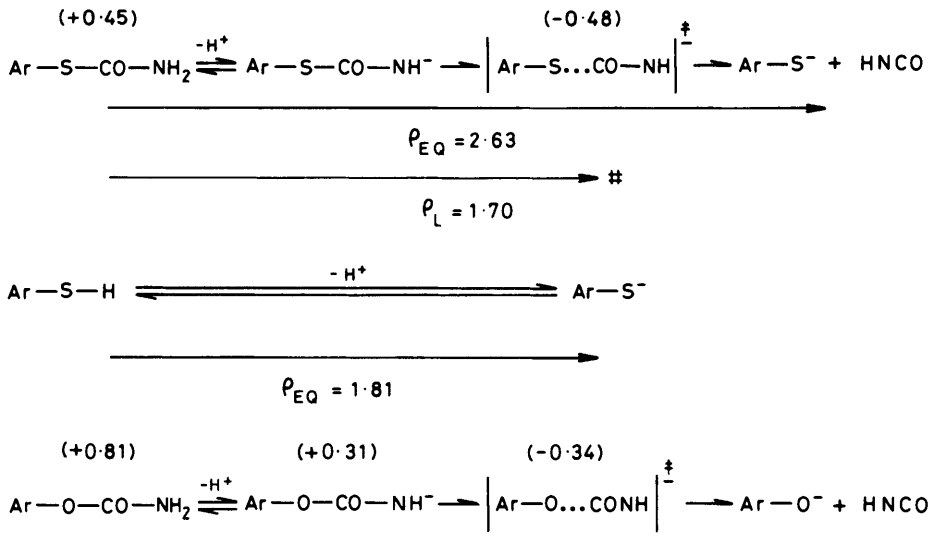


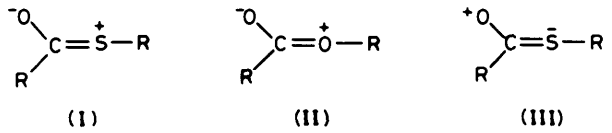
Figure 4. Effective charges on oxygen and sulphur in carbamate and thiocarbamate degradation

high polarity of the C=S bond in thiocarbamates.[2] There is no evidence from i.r. or ^{1}H n.m.r. studies[11] that structures of type (**III**) are involved in thioesters; this is curious to note because it might be expected that the empty sulphur 3*d* orbitals would accept electrons from the filled π-orbitals on the C=O. Indeed such overlap is suggested to account for carbanion stabilisation.[8d] We suggest that although the symmetry requirements and the coefficients of the orbitals may be favourable for overlap the absence of structures such as (**III**) could arise from too large a difference in energies of the appropriate molecular and atomic orbitals.

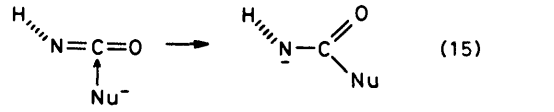
A similar difference in effective charge on oxygen and sulphur has been noted for acetates and thioacetates.[3] The high positive effective charge on nitrogen in acetylpyridines (+0.6)[12] where a structure like (**I**) or (**II**) is impossible is presumably due to good overlap of the *p* orbitals on the carbonyl with the π orbitals of the pyridine. Substituent effects will therefore be transmitted easily through the π system from the pyridine nucleus.

The stereochemistry of the elimination reaction can be either 'skewed' with the microscopic reverse involving attack of nucleophile perpendicular to the plane of the isocyanate or 'planar' [equations (15) and (16)]. The isocyanate possesses two almost degenerate lowest vacant molecular orbitals (LUMO)[13] to accept a donor orbital (HOMO) from the nucleophile. The symmetry and coefficients of these LUMOs is such to allow either 'in-plane' (16) or 'out-of-plane' (15) attack. The product anion stability for 'in-plane' attack is likely to be more favourable than that for 'out-of-plane' attack because the planar anion will possess resonance energy not present in the skewed form. The difference in energy of skewed and planar anions should resemble or exceed that for the not inconsiderable energy of C–N rotation in an amide.[14,15]* CNDO/2

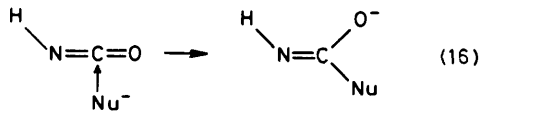
* In order to check that the CNDO/2 calculations were reasonable for this type of model we calculated the rotational energy for a model amide (formamide; 18.6 kcal mol^{-1}) and this came close to the experimental values.[14,15]



(I) (II) (III)



(15)

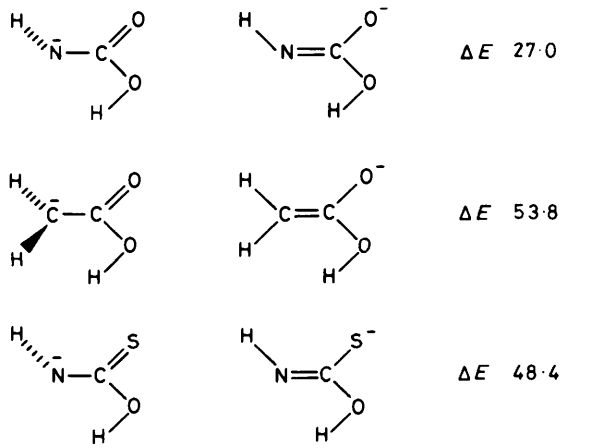


(16)

calculations on skewed and planar models of the product in equations (15) and (16) indicate an energy difference of *ca.* 27 kcal mol $^{-1}$; thus attack of the nucleophile at the central carbon, perpendicular to the plane of the isocyanate, is strongly retarded and by the principle of microscopic reversibility the stereochemistry of the elimination must be from the *planar* form.

The problem of the stereochemistry of *E*1cB reactions is general and Bruice has assumed that in the case of ketene formation from carbanions the latter react in their 'skewed' form.[16]

Calculations of the rotation energy of the carbanion model indicate a larger value (53.8 kcal mol $^{-1}$) than in the carbamate case; this difference may arise from overlap between the carbonyl π orbitals and the nitrogen lone pair in the 'skewed' conformer whereas no such stabilisation is possible in the carbanion case. The reaction of the carbanion should therefore be from the planar conformer and this is confirmed by consideration of the microscopic reverse where the LUMO of the ketene on the central carbon is 'in-plane'.[13] Molecular orbital studies with ketenes conjugated with π systems[17,18] indicate that a vacant π orbital on the central carbon perpendicular to the plane of the molecule can become almost degenerate with the 'in-plane' vacant orbital and even become the LUMO. Attack will then be most favourable from the *perpendicular* direction and may even be favoured by steric hindrance to 'in-plane' attack. The carbanion from this



Models for CNDO/2 calculations

stereochemistry will be skewed and if the interactions from the π system are strong enough the anion will not need to be planar with the carbonyl function for it to be stabilised.

We can conclude that non-conjugated ketenes, isocyanates, and isothiocyanates[2] add to give the planar anion and that the microscopic reverse, namely the *E*1cB reaction, has planar stereochemistry. Considerations for conjugated heterocumulenes must include factors such as steric hindrance and the value of the coefficient of the vacant orbital on the acceptor carbon. There seems to be no general rule governing the stereochemistry for the reactions of the conjugated systems.

Acknowledgements

We thank the S.E.R.C. for financial support of this work and Drs. A. D. C. Towl and T. Dickens for help with the molecular orbital calculations.

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Received 5th March 1984; *Paper* 4/359