

The S_N Mechanism in Aromatic Compounds. Part XXXIX.¹ Halogen Mobility and Reagent Strength in Reactions of Some Heavy Atom Neutral Nucleophiles (Thiourea, *N*-Acetylthiourea, and Selenourea) with 1-Chloro- and 1-Fluoro-2,4-dinitrobenzenes

By J. Miller *† and H. W. Yeung, University of Hong Kong, Hong Kong

The rates, and some derived parameters, of reaction of three heavy atom neutral nucleophiles (thiourea, *N*-acetylthiourea, and selenourea) with 1-fluoro- and 1-chloro-2,4-dinitrobenzene are measured and used to estimate (a) the mobilities of fluorine relative to chlorine, an important mechanistic feature of the usual (addition-elimination) S_NAr reactions; and (b) the strength of the reagents. Results are compared with those for a range of neutral and anionic light (Periodic Table first row) and heavy atom (Periodic Table second or higher row) nucleophiles. Results for 1-iodo-2,4-dinitrobenzene are included where available. A marked reduction in F:Cl mobility ratios (which are matched by F:heavy halogen ratios), well known in following a sequence from light to heavy atom anionic nucleophiles, is now shown to occur also with neutral nucleophiles.

ALTHOUGH the formation of thiuronium and analogous salts has been known for a long time,²⁻⁶ there appear to have been no measurements of rates and activation parameters of such reactions using activated aryl halides as substrates.

The present work reports such measurements, and leads to values of leaving group mobility of fluorine relative to chlorine with three heavy atom neutral nucleophiles; and permits comparisons of the strength of the nucleophiles with some common reagents. The leaving group mobility patterns are compared with those found with anionic nucleophiles, which are now well known.⁷

Urea (and derivatives) were excluded from this study since the nitrogen and not the Group VI atom (oxygen) is the nucleophilic centre.⁸

EXPERIMENTAL

Materials.—Absolute methanol was obtained from AnalaR methanol by refluxing with magnesium turnings followed by fractional distillation. The fraction boiling at 64.5° was collected.

Commercial 1-fluoro-2,4-dinitrobenzene was distilled

† *Present address:* Universidade Estadual de Campinas, 13,100 Campinas, S. P., Brasil.

¹ Part XXXVIII, J. Miller, *Austral. J. Chem.*, 1969, **22**, 921.

² A. Claus, *Annalen*, 1875, **179**, 145.

³ J. Taylor and A. E. Dixon, *J. Chem. Soc.*, 1924, **125**, 243.

⁴ M. Jureček and M. Večera, *Chem. Listy*, 1953, **47**, 274 and 1342.

under reduced pressure. The fraction of b.p. 163—164° at 11 mmHg was collected and formed crystals, m.p. 26° (lit.,⁹ 25-3°). Commercial 1-chloro-2,4-dinitrobenzene was repeatedly crystallised from ethanol to give crystals, m.p. 50.5° (lit.,⁹ 51°).

Commercial thiourea was recrystallised from ethanol to m.p. 178° (lit.,⁹ 180°). *N*-Acetylthiourea was obtained by acetylating thiourea with Ac₂O at ambient temperature (one week). Transparent crystals were obtained and recrystallised from acetic acid to give a product of m.p. 164° (lit.,¹⁰ 166°). Commercial selenourea was recrystallised from water, filtered under nitrogen, and vacuum dried over calcium chloride. The product had m.p. 200° (decomp.) [lit.,⁹ 200° (decomp.)].

Rates were obtained by standard procedures following determination of aliquot portions of fluoride or chloride ion produced in the reactions. Substrate and reagent were usually equimolar in concentration and in the range 0.015—0.04M. Fluoride ion was determined by titration with thorium nitrate in aliquot solutions buffered to pH 4, using Alizarin as indicator. Chloride ion was determined by potentiometric titration. After quenching with 2N-H₂SO₄ interfering sulphur compounds were oxidised with sufficient 2N-KMnO₄. For the reaction of selenourea, the quenched

⁵ E. Rosenhauer, H. Hoffmann, and W. Heuser, *Ber.*, 1929, **62B**, 2730.

⁶ J. S. Warner and T. F. Page, *J. Org. Chem.*, 1966, **31**, 606.

⁷ J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, London, and New York, 1968, chs. 5 and 6.

⁸ M. F. Buhler, *Anales asoc. quim. Argentina*, 1950, **38**, 252.

⁹ 'Dictionary of Organic Compounds,' 4th edn. (and supplements), Eyre and Spottiswoode, London, 1965.

¹⁰ A. E. Dixon and J. Hawthorne, *J. Chem. Soc.*, 1907, **91**, 122.

TABLE 1

Rate constants (k_2 /l mol⁻¹ s⁻¹) at temperatures (°C) given in parentheses, of reaction of thiourea, *N*-acetylthiourea, and selenourea with 1-fluoro- and 1-chloro-2,4-dinitrobenzene in methanol

Reagent	Leaving group in 1-halogeno-2,4-dinitrobenzene	
	F	Cl
$\text{NH}_2 \begin{array}{l} \diagup \\ \text{C}=\text{S} \\ \diagdown \end{array}$	$4.6_3 \times 10^{-4}$ (60.0)	$3.2_7 \times 10^{-4}$ (90.2)
	$9.7_5 \times 10^{-4}$ (70.0)	$4.9_2 \times 10^{-4}$ (96.5)
	$1.2_8 \times 10^{-3}$ (75.0)	$6.2_9 \times 10^{-4}$ (100.0)
	$1.8_6 \times 10^{-3}$ (80.0)	$8.2_5 \times 10^{-4}$ (105.2)
	$2.5_0 \times 10^{-3}$ (85.0)	$1.7_7 \times 10^{-3}$ (116.7)
$\text{AcNH} \begin{array}{l} \diagup \\ \text{C}=\text{S} \\ \diagdown \\ \text{NH}_2 \end{array}$	$3.9_3 \times 10^{-4}$ (79.9)	$7.3_6 \times 10^{-5}$ (120.5)
	$9.0_9 \times 10^{-4}$ (90.2)	$1.7_2 \times 10^{-4}$ (134.5)
	$1.6_7 \times 10^{-3}$ (99.8)	$2.7_6 \times 10^{-4}$ (142.3)
	$2.8_7 \times 10^{-3}$ (111.5)	$4.3_7 \times 10^{-4}$ (150.0)
	$4.2_6 \times 10^{-3}$ (119.9)	
$\text{NH}_2 \begin{array}{l} \diagup \\ \text{C}=\text{Se} \\ \diagdown \end{array}$	$2.9_6 \times 10^{-3}$ (72.0)	$3.9_1 \times 10^{-3}$ (90.4)
	$4.1_8 \times 10^{-3}$ (80.2)	$6.0_4 \times 10^{-3}$ (100.0)
	$9.5_2 \times 10^{-3}$ (90.2)	$1.0_2 \times 10^{-2}$ (109.1)

solution was extracted with ether before oxidation, which was carried out with a mixture of 6*N*-HNO₃ and 2*N*-KMnO₄.

Table 1 summarises the experimental data. Table 2 includes derived data, plus some corresponding results for

Estimated errors are k_2 , $\pm 1.5\%$; ΔE^\ddagger , ± 1.5 kJ mol⁻¹; and ΔS^\ddagger , ± 1.5 J mol⁻¹ K⁻¹. Second-order and Arrhenius plots are straight lines.

RESULTS AND DISCUSSION

Marked changes in mobility of fluorine relative to the heavy halogens in typical activated (addition-elimination) S_N2Ar reactions have been related to whether or not the formation of the first or second transition state (T.St.1 or T.St.2), which flank the intermediate or σ -complex, is rate-limiting.⁷ The changes have been satisfactorily correlated with potential energy-reaction co-ordinate profiles obtained by a semi-empirical theoretical procedure.^{7,11}

Where these profiles indicate that the formation of T.St.1 is rate-limiting in displacement of *all* the halogens, it is found experimentally that the mobility of fluorine is highest. In the typical pattern, the mobility of fluorine is quite large relative to the heavy halogens (10²–10³ at 50°) and correlates with the ΔE^\ddagger differences of F compared with Cl, Br, or I of *ca.* 12–20 kJ mol⁻¹ (3–5 kcal mol⁻¹).

The high reactivity of fluorine relative to the heavy

TABLE 2

Comparative kinetic data for reactions of 1-fluoro-, 1-chloro-, and/or 1-iodo-2,4-dinitrobenzene with some nucleophiles* at 50° in methanol, unless otherwise specified

Reagent	Leaving group	k_2 / l mol ⁻¹ s ⁻¹	Activation energy		Fre- quency factor log ₁₀ B l mol ⁻¹ s ⁻¹	Activation entropy		RT - TΔS [‡] kJ mol ⁻¹	Activation free energy ΔG [‡] = ΔE [‡]	Nucleophilic rate ratio relative to		Leaving group mobility relative to	
			ΔE [‡] kJ mol ⁻¹	ΔΔE [‡]		ΔS [‡] / J mol ⁻¹ K ⁻¹	-TΔS [‡] kJ mol ⁻¹			(a) OMe ⁻ = 1	(b) Thiourea = 1	(a) Cl = 1	(b) I = 1
OMe ⁻	F	$8.1_3 \times 10^1$	56.5	0	11.1	-41.4	13.4	67.3	1	$3.9_3 \times 10^5$	$2.8_1 \times 10^2$	$1.1_3 \times 10^3$	
	Cl	$2.8_3 \times 10^{-1}$	73.2	+16.7	11.2	-37.7	12.3	82.7	1	$2.0_4 \times 10^4$	1	4.1_3	
	I	$6.8_3 \times 10^{-2}$	79.5	+23.0	11.7	-29.7	9.6	86.4	1	1	$2.3_8 \times 10^{-1}$	1	
NH ₃	F	$1.9_7 \times 10^{-2}$	50.0	0	7.1	-118	38.1	86.0	$2.3_3 \times 10^{-4}$	$9.1_4 \times 10^1$	$1.1_2 \times 10^5$	$3.4_5 \times 10^3$	
	Cl	$1.7_0 \times 10^{-5}$	69.5	+18.5	6.5	-130	42.0	109	$5.9_3 \times 10^{-5}$	1.2 ₁	1	3.0_3	
	I	$5.6_3 \times 10^{-4}$	71.0	+20.4	6.4	-131	42.3	111	$8.2_0 \times 10^{-5}$	1	$3.3_0 \times 10^{-1}$	1	
PhNH ₂ in EtOH at 50°	F	$1.6_3 \times 10^{-2}$	26.8	0	2.3	-204	65.9	90.0	<i>ca.</i> 10 ⁻⁴	<i>ca.</i> 5 × 10 ¹	$6.2_5 \times 10^1$	$1.2_3 \times 10^2$	
	Cl	$2.6_3 \times 10^{-4}$	46.9	+20.1	4.0	-177	57.2	101	<i>ca.</i> 5 × 10 ⁻⁴	<i>ca.</i> 10 ¹	1	2.0_5	
	I	$1.3_1 \times 10^{-4}$							<i>ca.</i> 10 ⁻³	1	$4.8_7 \times 10^{-1}$	1	
PhNHMe in EtOH at 67.2°	F	$7.3_3 \times 10^{-5}$							<i>ca.</i> 5 × 10 ⁻⁷	<i>ca.</i> 2 × 10 ⁻¹	1.0		
	Cl	$7.3_0 \times 10^{-5}$							<i>ca.</i> 2 × 10 ⁻⁴	<i>ca.</i> 3	1		
SPH ⁻	F	$2.5_2 \times 10^3$	44.8	0	10.5	-52.7	17.0	59.1	$3.0_3 \times 10^1$	$1.2_1 \times 10^7$	$3.4_3 \times 10^1$	$2.3_1 \times 10^1$	
	Cl	$7.3_4 \times 10^1$	43.1	-1.7	8.9	-83.7	27.1	67.5	$2.5_3 \times 10^2$	$5.2_1 \times 10^6$	1	$6.7_3 \times 10^{-1}$	
	I	$1.0_8 \times 10^2$	44.8	0	9.3	-75.7	24.5	66.6	$1.5_3 \times 10^2$	1	1.4_3	1	
$\text{NH}_2 \begin{array}{l} \diagup \\ \text{C}=\text{S} \\ \diagdown \end{array}$	F	$2.0_9 \times 10^{-4}$	67.8	0	7.3	-114	36.8	102	$2.5_5 \times 10^{-6}$	1	$1.4_8 \times 10^1$		
	Cl	$1.4_1 \times 10^{-5}$	76.6	+8.8	7.5	-110	35.6	109	$4.9_0 \times 10^{-5}$	1	1		
$\text{AcNH} \begin{array}{l} \diagup \\ \text{C}=\text{S} \\ \diagdown \\ \text{NH}_2 \end{array}$	F	$3.8_3 \times 10^{-5}$	72.4	0	7.3	-114	36.8	107	$4.7_5 \times 10^{-7}$	$1.8_8 \times 10^{-1}$	$1.0_7 \times 10^2$		
	Cl	$3.6_3 \times 10^{-7}$	83.3	+10.9	6.9	-122	39.4	120	$1.2_6 \times 10^{-6}$	$2.5_7 \times 10^{-2}$	1		
$\text{NH}_2 \begin{array}{l} \diagup \\ \text{C}=\text{Se} \\ \diagdown \end{array}$	F	$5.3_7 \times 10^{-4}$	67.4	0	7.8	-108	34.9	99.8	$6.5_8 \times 10^{-6}$	2.5 ₇	1.7		
	Cl	$3.0_3 \times 10^{-5}$	60.2	-7.2	6.3	-135	43.3	101	$1.0_7 \times 10^{-5}$	$2.1_3 \times 10^1$	1		
SCN ⁻	F	Probably <10 ⁻³	†									Probably <10 ⁻³	
	I	$5.0_5 \times 10^{-5}$	84.1		9.3	-75.7	24.5	106			1	Probably <10 ⁻⁴	
I ⁻	F	Probably <10 ⁻¹¹	†									Probably <10 ⁻⁴	
	I	$4.0_3 \times 10^{-7}$	95.4		9.1	-80.8	26.1	119			1		

* Results now presented and quoted in ref. 7. † ΔE[‡] For iodo-compound probably at least 30 kJ mol⁻¹ lower than the value for the fluoro-compound.

other reagents. In addition 1-iodo-2,4-dinitrobenzene has been included as a comparison substrate.

¹¹ (a) J. Miller, *J. Amer. Chem. Soc.*, 1963, **85**, 1628; (b) *J. Chem. Soc. (B)* 1966, 299.

halogens, as well as absolutely, has been ascribed to the increase in electrophilic strength of the carbon atom, at which reaction occurs, resulting from the high electro-negativity of the attached fluorine.

Common light nucleophiles* such as hydroxide, alkoxide, aryloxide, and azide ions; water and alcohols; aliphatic amines; and aromatic primary amines are reagents in activated S_NAr reactions with which fluorine is the most mobile of the halogens.⁷ In contrast, it is known that with heavy anionic nucleophiles generally, *e.g.* iodide and thiocyanate ions, fluorine has low mobility relative to the heavy halogens.⁷ Highly reactive heavy anionic nucleophiles fall in or near a border region between light and heavy nucleophile behaviour with the pattern likely to be obscured by entropy factors ($\log_{10} B/\Delta S^\ddagger$ controlled). Alkylated anilines also appear to be in a border region, known with certainty for *N*-methylaniline.^{7,12,13} These comments may be generally applied only to reactions in protic solvents; but have also been observed in reactions in highly dipolar aprotic solvents.^{7,14}

Table 2 illustrates these patterns by inclusion of results for reactions of 1-fluoro- and 1-chloro-, plus 1-iodo-2,4-dinitrobenzene (where available) with methoxide, phenylthiolate, thiocyanate, and iodide ion in methanol; of ammonia in methanol, and of aniline and *N*-methylaniline in ethanol. Table 2 also includes data based on the new results of Table 1. The Figure shows the P.E.-reaction co-ordinate profiles for the three halogenoaromatic substrates in their reactions with methoxide, phenylthiolate, and iodide ions; and with aniline and *N*-methylaniline.

From Table 2, the F : Cl and F : I ratios are 289 and 1190 for methoxide ion; 1120 and 3400 for ammonia; and 62.5 and 128 for aniline. The somewhat lower ratios for aniline illustrate the incursion of entropy factors since the $\Delta\Delta E^\ddagger$ value is typical. The very negative value of ΔS^\ddagger (smaller $\log_{10} B$) in displacement of fluorine by aniline was ascribed by the original workers to solvation factors.¹⁵

A shift towards T.St.2 formation as rate-limiting in displacement of fluorine should become evident in considering a sequence of reactions in which the level of the I.St. drops relative to the F.St. *i.e.* ΔH° (and also ΔG°) less exothermic. It is expected to be evident much more readily in displacement of fluorine than the heavy halogens, because the very strong carbon-fluorine bond makes the level of T.St.2 relatively high. It is worth interpolating that the ΔH° values for displacement of all the halogens differ by little, reflecting cancellation of energy terms which differ considerably.

The shift is expected to occur more readily in the sequence where the nucleophile-carbon bond is relatively

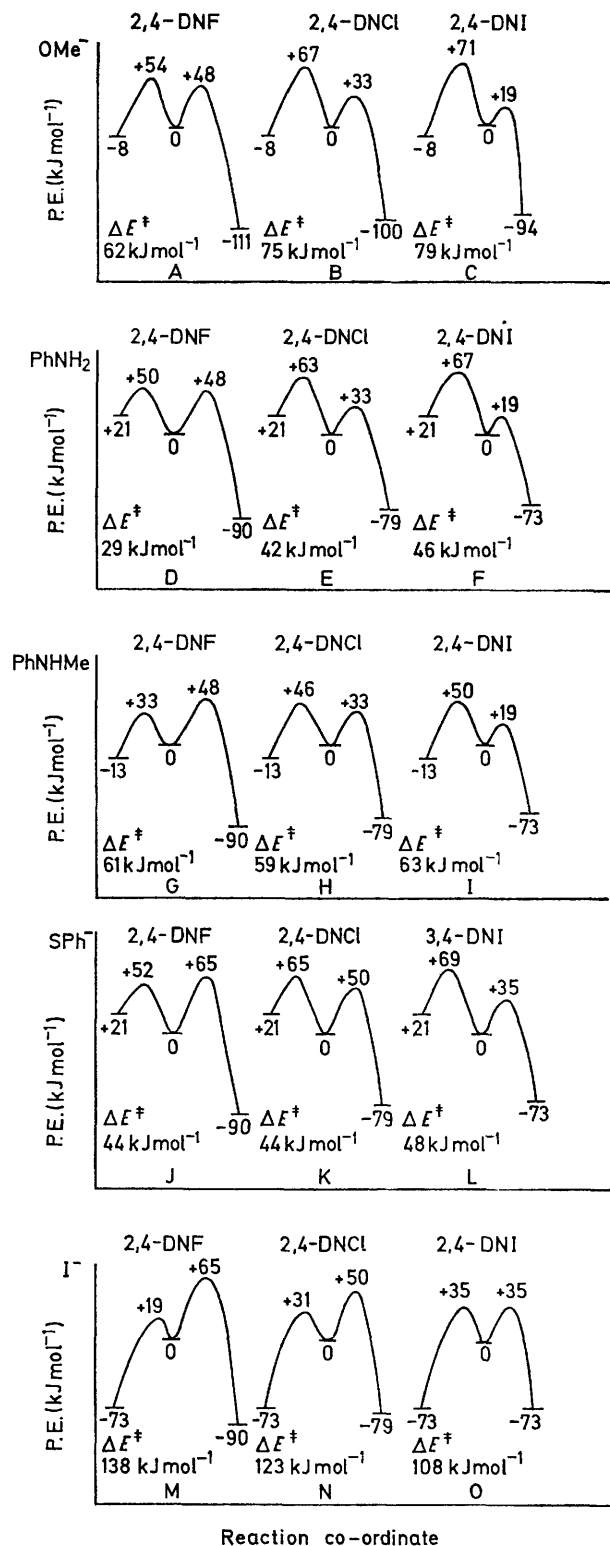
* Nucleophiles in which the nucleophilic atom is in the first row of the Periodic Table. Correspondingly, heavy nucleophiles are those in which the nucleophilic atom is in the second or higher row of the Periodic Table.

¹² G. S. Hammond and L. R. Parks, *J. Amer. Chem. Soc.*, 1955, **77**, 340.

¹³ J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.*, 1958, **80**, 6020.

¹⁴ J. Miller and A. J. Parker, *J. Amer. Chem. Soc.*, 1961, **83**, 117.

¹⁵ N. B. Chapman and R. E. Parker, *J. Chem. Soc.*, 1951, 3301.



P.E.-reactions co-ordinate profiles for reaction of 1-fluoro- (2,4-DNF), 1-chloro- (2,4-DNCl), and 1-iodo-2,4-dinitrobenzene (2,4-DNI) with OMe^- (A, B, C); $PhNH_2$ (D, E, F); $PhNHMe$ (G, H, I); SPh^- (J, K, L); and I^- (M, N, O)

weak, since this would be reflected in relatively low values of T.St.1.

It is unfortunate that there are insufficient data for the semi-empirical calculation of P.E.-reaction co-ordinate profiles. Nevertheless the experimental data are very significant in relation to the discussion of such profiles, and comments made above.

It seemed reasonable that the spectrum of halogen mobility patterns found in reactions of activated aryl halides with anionic nucleophiles, especially comparing light and heavy nucleophiles, might be found also in reactions of light and heavy neutral nucleophiles. The present results provide evidence for such patterns.

With thiourea, the F : Cl ratio is only 14.8. It is due almost entirely to the $\Delta\Delta E^\ddagger$ value being only 8.7 kJ mol⁻¹, about half the value typical with light anionic and neutral nucleophiles. Our earlier discussion⁷ leads us to suggest that this is because the formation of T.St.2 is rate-limiting in displacement of fluorine, though not of chlorine; but that the difference T.St.2 - T.St.1 is only about 6-9 kJ mol⁻¹. With the chloro-compound T.St.1 formation should be rate-limiting but with T.St.1 for the chloro-compound *ca.* 12-18 kJ mol⁻¹ higher than T.St.1 for the fluoro-compound, reflecting the electronegativity effect. This would lead to the observed result. An experimental ΔE^\ddagger pattern of this nature agreeing with predicted P.E.-reaction co-ordinate profiles, was found in reactions of methylthiolate ion with *p*-fluoro- and *p*-iodo-nitrobenzenes.¹⁶ The mobility pattern was nevertheless not the same as with thiourea because a heavy nucleophile interaction reduces the mobility of chlorine but not of fluorine in reactions with methylthiolate ion in a protic solvent.

The experimental results for selenourea though differing from those for thiourea further support the above discussion. Comparing thiourea and selenourea in their reactions with 1-fluoro- and 1-chloro-2,4-dinitrobenzene one would confidently predict for the pair of reactions with the latter reagent a $\Delta\Delta E^\ddagger$ value either favouring fluorine displacement less or even favouring chlorine displacement. This is what is observed. With thiourea, ΔE^\ddagger for the fluoro-compound is 8.7 kJ mol⁻¹ lower than for the chloro-compound, as mentioned above. With selenourea the value of ΔE^\ddagger for the fluoro-compound is actually 7.1 kJ mol⁻¹ higher than that for the chloro-compound. In this pair of reactions but not with the pair of thiourea reactions the entropy of activation is significantly more negative for the chloro- than the fluoro-compound. The F : Cl ratio is close to, but not less than, unity (actually 1.74) but this is entropy not enthalpy dependent.

The difference in mobility patterns observed in comparing thiourea and selenourea reactions is thus in the expected direction; and correlates with the (assumed) weaker selenium-carbon than sulphur-carbon bond in the 'onium salts.

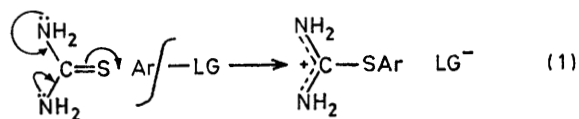
While mildly differentiated by the entropy term, the

results with *N*-acetylthiourea show that the halogen mobility pattern is similar to that with thiourea.

It remains to comment on the kinetic nucleophilic strength of these second and third row urea derivatives. These are based on an approach found successful in earlier papers on S_NAr reactions,⁷ though not confined to such reactions. It has been elaborated recently.¹⁷

This is best done here in the reactions with 1-chloro-2,4-dinitrobenzene, for which we can have reasonable confidence that the bond-forming step (forming T.St.1) is rate-limiting; and thus rupture of the bond to the leaving group does not influence the strength of the reagent as a nucleophile.

Thiourea has higher nucleophilic strength than simple thiones as a result of the conjugation of the amino with the thiocarbonyl function [process (1)]. This is accentuated by there being two equivalent amino-groups which



share the positive charge. The higher reactivity compared with simple thiones may be correlated with the first ionisation energy differences. Thus, *e.g.* the first ionisation energy of thiourea is *ca.* 92 kJ mol⁻¹ less than that of thioformaldehyde.^{18,19}

There is some value in a comparison with ammonia which has about the same nucleophilic strength as thiourea towards 1-chloro-2,4-dinitrobenzene. Thiourea has the lower value of the first ionisation energy, comparable in fact with primary and secondary aliphatic amines, and this alone corresponds to higher reactivity of thiourea. However, expected adverse factors in contrast are the (assumed) weaker C-S than C-N bond; and lower solvation energy of T.St.1 in forming a thio-urionium than ammonium salt. The resultant is consistent with the experimentally observed approximate equality.

In *N*-acetylthiourea the competitive alternative conjugation for the unshared electrons of nitrogen in the acetyl-amino-group should result in a reduction in nucleophilic strength compared with thiourea. This is experimentally observed, the rate constant at 50° being about 40 times smaller for reaction of *N*-acetylthiourea with 1-chloro-2,4-dinitrobenzene. In the main this is due to a higher value of ΔE^\ddagger for *N*-acetylthiourea, but a more negative ΔS^\ddagger value also contributes to the difference.

Selenourea is considerably more nucleophilic than thiourea: the rate constant ratio in reaction with 1-chloro-2,4-dinitrobenzene is 21.9. The (assumed) weaker C-Se than C-S bond corresponds to the opposite order. On the other hand we would expect the first ionisation energy of selenourea to be substantially less than that of thiourea and the higher reactivity of selenourea to

¹⁶ K. C. Ho, J. Miller, and K. W. Wong, *J. Chem. Soc. (B)*, 1966, 310.

¹⁷ J. Miller, *Ciência e Cultura*, 1972, 24, 11.

¹⁸ A. Jones and F. P. Lossing, *J. Phys. Chem.*, 1967, 71, 4111.
¹⁹ A. Maccoll, A. Kirkién-Konasiewicz, and B. Saville, *Chem. and Ind.*, 1966, 286.

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correlate with this, as having greater weight. Correspondingly the higher reactivity of neutral nitrogen than corresponding oxygen nucleophiles and of neutral sulphur than corresponding oxygen nucleophiles may be correlated with ionisation energy differences.⁷

The value of ΔS^\ddagger for the three second and third row

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urea reagents are at the upper end of the range typical of reactions of neutral nucleophiles with neutral aromatic substrates. Possibly the dispersed positive charge in the forming 'onium salts, as it affects the solvation entropy, is responsible for the relatively high ΔS^\ddagger values.

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