Theoretical studies on the reactivity of phenylthiocyanates

John O. Morley and Memdoh Naji

Chemistry Department, University of Wales Swansea, Singleton Park, Swansea, UK SA2 8PP

Molecular orbital calculations are reported on the electronic structure of phenylthiocyanate and its 4-nitro and 4-amino derivatives using the semi-empirical AM1 and PM3 methods. The reactivity of these systems at the cyano carbon, sulfur atom and aryl carbon have been explored with the methoxide ion in methanol using the AM1/COSMO method. In terms of overall stability, attack at the aryl carbon with the displacement of the thiocyanate anion is the preferred process in all three cases followed by the alternative attack at the cyano carbon resulting in the displacement of the phenylthiolate anion: the corresponding attack at the sulfur atom with the displacement of the cyanide ion is strongly disfavoured. Kinetically, the reaction selectivity is highly dependent on the substituent present though all three molecules readily form reversible complexes at the sulfur atom. The activation energies suggest that 4-nitrophenylthiocyanate will react at both the aryl carbon or cyano carbon, but phenylthiocyanate and 4-aminophenylthiocyanate would be expected to react preferentially at the cyano carbon only.

Introduction

Organic phenylthiocyanates are examples of trifunctional electrophiles[1,2] which are attacked readily by a variety of nucleophiles either at the cyano carbon resulting in displacement of the phenylthiolate ion [eqn. (1)], or at the sulfur atom resulting in the displacement of the cyanide ion [eqn. (2)], or at the aromatic ring resulting in the displacement of the thiocyanate ion [eqn. (3)].[1,2]

$$\mathrm{ArSCN + X^- \longrightarrow ArS^- + XCN} \qquad (1)$$

$$\mathrm{ArSCN + X^- \longrightarrow ArSX + CN^-} \qquad (2)$$

$$\mathrm{ArSCN + X^- \longrightarrow ArX + SCN^-} \qquad (3)$$

The products obtained from these reactions are not straightforward because the initial products formed are able to react further either with the original nucleophile or the displaced anion. This is particularly true of reaction (2), where the initial product may be further attacked to liberate the phenylthiolate anion [eqns. (4) and (5)].

$$\mathrm{ArSX + X^- \longrightarrow ArS^- + XX} \qquad (4)$$

$$\mathrm{ArSX + CN^- \longrightarrow ArS^- + XCN} \qquad (5)$$

However, the degree of attack at a given atomic centre is highly dependent on the number and nature of substituents present in the phenyl ring. For example, in non-aqueous solvents, nucleophiles such as phenylthiolate or azide ion attack phenylthiocyanate (**1a**) and its 4-nitro derivative (**1b**) at the cyano carbon displacing the phenylthiolate ion[2] in line with eqn. (1), while 2,4,6-trinitrophenylthiocyanate (**1d**) is attacked at the aryl carbon resulting in the displacement of the thiocyanate anion[1-3] in line with eqn. (3).

2,4-Dinitrophenylthiocyanate (**1e**) reacts in a similar way to the trinitro-derivative (**1d**) with phenylthiolate or azide ions resulting in the displacement of the thiocyanate anion (eqn. 3), but ethane thiolate reacts differently. In this case, the product is thought to arise from an initial attack at sulfur to give ethyl 2,4-dinitrophenyldisulfide [eqn. (2)] followed by its subsequent reaction with the nucleophile to give 2,4-dinitrophenylthiolate [eqns. (4) or (5)].

In water, alkyl thiocyanates readily liberate cyanide in the presence of alkyl thiols[4] supporting eqn. (2), but more detailed studies on 2-nitro-5-thiocyanobenzoic acid (**1f**) suggest that the liberation of cyanide occurs by a more complex mechanism which involves the initial displacement of 2-nitro-5-sulfidobenzoic acid [eqn. (1)] and its subsequent reaction with the starting thiocyanate to give a symmetrical disulfide [eqn. (6)].[5,6]

$$\mathrm{ArSCN + ArS^- \longrightarrow ArSSAr + CN^-} \qquad (6)$$

In contrast, the reaction of tetraphenylarsonium ^{13}C-cyanide with 4-nitrophenylthiocyanate (**1b**) in acetonitrile results in a rapid exchange of the cyano group in line with eqn. (2) followed by the formation of a stable adduct [eqn. (7)].[7]

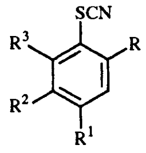
$$\mathrm{ArSCN + 2CN^- \longrightarrow ArS(CN)_3{}^{2-}} \qquad (7)$$

The nucleophilic reactions of phenylthiocyanates are therefore considerably more complex than those involving related systems such as phenyl, benzoyl and benzenesulfonyl halides and esters where electron donors retard the reaction and electron attractors facilitate attack at a single atomic centre.[8,9] Although there have been a number of theoretical studies of aromatic substituent effects at one reactive centre which are consistent with experimental data,[10] the corresponding effects at the three reactive centres of the phenylthiocyanates have received much less attention with the exception of two recent studies on phenylthiocyanate itself (**1a**)[11] and its 2-nitro derivative (**1g**).[12]

The calculations reported here have been carried out to probe the effect of ring substituents on the electronic properties and the reactivity pattern of phenylthiocyanate (**1a**) using as examples the electron attracting 4-nitro group to give structure (**1b**) and the electron donating 4-amino group to give structure (**1c**), respectively. Additionally, the nucleophilic reactions of the three phenylthiocyanates (**1a–c**) have been explored with a representative nucleophile in solvent using a semi-empirical continuum approach along the reaction coordinate. In these studies we have used the methoxide ion as a typical nucleophile with methanol as the reaction solvent.

Methods of calculation

Calculations were carried out with full geometry optimisation on phenylthiocyanate (**1a**) and the 4-nitro (**1b**) and 4-amino (**1c**) derivatives using both the semiempirical AM1[13] and PM3[14]



1

- **a** $R = R^1 = R^2 = R^3 = H$
- **b** $R = R^2 = R^3 = H; R^1 = NO_2$
- **c** $R = R^2 = R^3 = H; R^1 = NH_2$
- **d** $R^2 = H; R = R^1 = R^3 = NO_2$
- **e** $R^2 = R^3 = H; R = R^1 = NO_2$
- **f** $R = R^3 = H; R^1 = NO_2; R^2 = CO_2H$
- **g** $R^1 = R^2 = R^3 = H; R = NO_2$

methods of the MOPAC program.[15] Nucleophilic reactions of the phenylthiocyanates (**1a**), (**1b**) and (**1c**) were carried out using the COSMO method[16] implemented in the MOPAC[15] program at the AM1 level[13] (keywords: 'am1 precise xyz saddle eps = 32.6 charge = − 1'). The transition state was approached from both the reactants side of the reaction, with the methoxide anion placed perpendicularly at a distance of 10 Å from the reactive centre at the starting point, and from the products side of the reaction with the displaced anion again placed perpendicularly at a distance of 10 Å from the same reactive centre at the end of the reaction. The energy was evaluated as a function of the decreasing distance of the approaching or departing ion from either the cyano carbon, C8, sulfur atom, S7, or aryl carbon, C1, with the geometry fully optimised at each point. In most cases, two saddle points were found at each side of an intermediate along the reaction coordinate. Each transition state (TS1 and TS2) was refined and shown to be a first order saddle point by virtue of its unique single imaginary vibrational frequency. For the first transition state, the intrinsic reaction coordinate path (IRC) was followed both forwards to a stationary point for the intermediate and backwards to the reactants. The second transition state was characterised similarly by running the IRC backwards to the intermediate and forward to the products. The reaction sequences explored are illustrated in Schemes 1–3, and the atom labelling convention adopted for the calculations is shown in Fig. 1.

Results and discussion

1. Calculated structures and electronic properties

Experimentally, there are few structures available for the phenylthiocyanates for comparative purposes in the Cambridge Structural Database[17] with the exception of the highly relevant 4-amino derivative (**1c**).[18] Initial calculations were carried out to assess the potential of both the semi-empirical AM1[7] and PM3[8] methods to reproduce the experimental geometry of this structure (**1c**), in a similar way to our earlier study which used the AM1 and MNDO methods,[11] before analysing the electronic properties such as the partial charges at the aromatic carbon atom, sulfur atom and the cyano carbon atom of the phenylthiocyanates. The results from both calculations show similar trends in terms of the bond lengths and angles but the PM3 method gives a better account of the Ph–S and S–CN bond lengths relative to the crystal structure (Table 1). The calculated angles show a good correlation with experiment with the key Ph–S–CN angle only slightly overestimated by around 5° by both methods. However, while the PM3 method predicts a tetrahedral sp^3 amino group with the C3–C4–N10–H12 torsion angle at 29°, the value of 20° obtained by the AM1 method is closer to the experimental value of 16° (Table 1).

The structure of both the parent (**1a**) and the 4-nitro derivative (**1b**) show similar bond lengths to the 4-amino derivative (**1c**) at the aromatic ring and at the SCN group (Table 1). The AM1 results obtained here for phenylthiocyanate

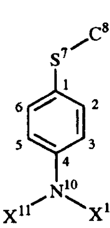


Fig. 1 Atom labelling convention adopted for the phenylthiocyanate (**1a**), 4-nitrophenylthiocyanate (**1b**, X = O) and 4-aminophenylthiocyanate (**1c**, X = H)

(**1a**) are similar to those we reported earlier[11] with the notable exception that the molecule is now predicted to be almost planar using the MOPAC 93 program (Table 1) whereas MOPAC Version 6 used in that study[11] gave a twisted structure with a slightly higher energy of 0.41 kcal mol^{-1} (1 cal = 4.184 J).

The calculated dipole moments show a reasonable correlation with experimental data (Table 2) with the PM3 method giving a better result for the 4-nitro derivative (**1b**) with value of 3.2 D *vs.* 3.1 D experimentally, while the AM1 method gives a better result for the 4-amino derivative (**1c**) with values here of 4.9 D *vs.* 5.2 D, respectively. The calculated charge distribution of phenylthiocyanate (**1a**) show the sulfur atom to be positively charged with the nitro and amino groups in (**1b**) and (**1c**) increasing and decreasing the magnitude of the charge respectively in line with their expected electron attracting and donating character (Table 2). The charge at the aryl carbon, C1, is negative, but ring substitution shows similar trends to those calculated at the sulfur atom with the nitro and amino groups reducing and increasing the value respectively (Table 2). In contrast, the negatively charged cyano carbon, C8, of the parent (**1a**) shows exactly the opposite trend with the nitro group surprisingly increasing the negative charge and the amino group showing the opposite effect though the magnitude of the change here is much smaller than the effects found at either the sulfur atom or aryl carbon (Table 2).

2. Reaction coordinate calculations

The energetics of the nucleophilic displacement reactions at the cyano carbon, C8 [eqn. (1), Scheme 1], sulfur atom, S7 [eqn. (2), Scheme 2] and aryl carbon, Cl [eqn. (3), Scheme 3], were explored using the COSMO method[16] (implemented in the MOPAC 93 program[15]), which is based on a continuum approach where the solute is embedded in a dielectric continuum of permittivity, ε. Although there appears to be little to choose between the AM1 and PM3 methods in terms of the predicted electronic properties, the former was selected because it gives a greater polarisation of charge at the key reactive centres (Table 2). The reactions were carried out between the respective phenylthiocyanate and the methoxide ion as a representative nucleophile with methanol as the continuum (ε = 32.6) and adopting the recommended number of segments per atom on the solvent accessible surface.[16]

The dielectric field exerted by methanol alone at the van der Waals surface of the respective phenylthiocyanate, produces a significant change in the molecular charge distribution. For phenylthiocyanate itself (**1a**), the atomic charges at the key C1, S7, C8 and N9 atoms change from −0.280, 0.530, −0.380 and 0.007 in the gas phase (Table 2) to −0.313, 0.566, −0.290 and −0.121, respectively, in methanol. The presence of solvent is likely therefore to have a considerable impact on the course of the nucleophilic substitution reaction.

The transition states of each reaction were approached from both sides of the reaction coordinate, with the methoxide ion initially placed perpendicularly at a distance of 10 Å either from the cyano carbon, C8 (Scheme 1), sulfur atom, S7 (Scheme 2) or aryl carbon, C1 (Scheme 3) at the starting point, and the

Table 1 Calculated geometries of 4-substituted phenylthiocyanates obtained using the AM1 and PM3 methods

	1a		**1b**		**1c**		
Parameter[a]	AM1	PM3	AM1	PM3	AM1	PM3	Expt.[b]
C1–C2	1.396	1.393	1.398	1.394	1.400	1.397	1.383
C2–C3	1.395	1.391	1.393	1.390	1.386	1.386	1.369
C3–C4	1.393	1.390	1.403	1.398	1.419	1.405	1.391
C4–C5	1.397	1.392	1.406	1.401	1.419	1.405	1.395
C5–C6	1.391	1.388	1.388	1.387	1.386	1.386	1.374
C6–C1	1.403	1.399	1.405	1.399	1.400	1.397	1.386
C1–S7	1.700	1.768	1.693	1.764	1.698	1.766	1.786
S7–C8	1.613	1.660	1.614	1.660	1.616	1.663	1.698
C8–N9	1.170	1.165	1.170	1.165	1.170	1.165	1.137
C4–N10			1.486	1.500	1.384	1.420	1.377
N10–X11			1.202	1.214	0.992	0.995	0.869
N10–X12			1.202	1.214	0.992	0.995	0.905
C1–C2–C3	120.2	119.9	120.7	120.4	121.2	120.5	120.4
C2–C3–C4	120.2	120.3	119.3	120.1	120.3	119.9	121.0
C3–C4–C5	119.8	119.9	120.7	119.7	118.3	119.6	118.1
C4–C5–C6	120.1	120.2	119.2	120.0	120.3	119.9	121.1
C5–C6–C1	120.2	120.0	120.7	120.4	121.2	120.5	119.8
C6–C1–C2	119.5	119.8	119.4	119.5	118.8	119.6	119.6
C2–C1–S7	126.3	125.8	126.3	126.0	120.4	120.2	120.2
C1–S7–C8	105.4	104.6	105.4	104.5	104.4	102.4	99.9
S7–C8–N9	176.3	176.0	176.2	175.8	177.00	177.0	178.6
C3–C4–N10			119.7	120.2	120.8	120.1	120.7
C4–N10–X12			118.9	119.3	116.8	112.6	116.7
X11–N10–X12			122.2	121.5	115.8	112.0	113.5
C2–C1–S7–C8	0.0	−0.3	−0.1	0.1	93.9	91.7	107.8
C3–C4–N10–X12			0.4	0.8	−19.9	−28.6	−16.4
$\Delta_f H$[c]	53.48	63.63	58.26	56.65	51.11	60.54	

[a] Bond lengths (Å), angles (°). [b] Ref. 18. [c] Heat of formation (kcal mol^{-1}).

Table 2 Calculated atomic charges and dipole moments of the phenylthiocyanates[a]

	1a		**1b**		**1c**	
Atom	AM1	PM3	AM1	PM3	AM1	PM3
C1	−0.280	−0.192	−0.247	−0.141	−0.378	−0.281
C2	−0.115	−0.086	−0.134	−0.115	−0.016	0.005
C3	−0.115	−0.088	−0.048	0.009	−0.224	−0.173
C4	−0.123	−0.089	−0.134	−0.404	0.127	−0.032
C5	−0.116	−0.091	−0.052	0.002	−0.224	−0.173
C6	−0.114	−0.072	−0.131	−0.099	−0.016	0.005
S7	0.536	0.365	0.577	0.393	0.492	0.342
C8	−0.380	−0.303	−0.394	−0.317	−0.372	−0.300
N9	0.007	−0.007	0.034	0.019	−0.018	−0.025
H2	0.143	0.118	0.158	0.129	0.144	0.117
H3	0.139	0.110	0.177	0.139	0.138	0.118
H4	0.137	0.108				
H5	0.138	0.109	0.177	0.138	0.138	0.118
H6	0.141	0.118	0.157	0.130	0.144	0.117
N10			0.569	1.307	−0.350	0.088
X11			−0.355	−0.594	0.207	0.038
X12			−0.354	−0.593	0.206	0.038
μ (calc.)	2.93	3.42	3.81	3.16	4.89	4.53
μ (expt.)	3.01[b]		3.10[d]		5.16[d]	
	3.62[c]		3.10[e]		5.22[e]	

[a] μ Is the dipole moment (D). [b] Ref. 19. [c] Ref. 20. [d] Ref. 21. [e] Ref. 22.

displaced arylthiolate, thiocyanate or cyanide ion placed respectively at a distance of 10 Å from the same atoms at the end of the reaction. Nucleophilic attack on each of the phenylthiocyanates is predicted to proceed in most cases *via* the formation of intermediates or ion pairs. The predicted saddle points of the three reactions are all higher in energy than the reactants or intermediates, but the magnitude reduces once these approximate structures are fully optimised. Each transition state was fully characterised by its unique single imaginary vibrational frequency for the reaction coordinate mode using the intrinsic reaction coordinate procedure in the MOPAC program (see Methods of calculation).

2.1 Attack at the cyano carbon (Scheme 1). Nucleophilic attack at the cyano carbon, C8 (Scheme 1), results in the formation of an intermediate (**2**) which thermodynamically is most stable for the 4-nitro derivative (**2b**) and least stable for the 4-amino derivative (**2c**) with values of 14.7 and 18.2 kcal mol^{-1} above the reactants, respectively, *vs.* 16.7 kcal mol^{-1} for phenylthiocyanate itself (**2a**) (Table 3, Fig. 2). However, as far as the activation energy of the addition is concerned, the substituents surprisingly appear to exert little influence on the course of the reaction, and the transition states (**TS1**) are 31.2 to 32.7 kcal mol^{-1} higher in energy than the reactants (Table 3, Fig. 2).

Table 3 Enthalpies of the reactions of phenylthiocyanates (**1**) with methoxide ion in methanol at the cyano group, transition state geometries and reaction coordinate vibrational frequencies, calculated using the AM1/COSMO method

				TS geometry[c]		Relative energy[d]		
	R^1	Coordinate position[a]	$\Delta_f H$[b]	MeO–CN	NC–SAr	δE_1	δE_2	Frequency[e]
1a	H	R	−88.83	∞	1.61	0		
		TS1	−57.63	1.82	1.67	31.17		617.9i
		2a	−72.19	1.40	1.89	16.69	0	
		TS2	−71.89	1.39	1.94		0.30	166.6i
		P	−91.77	1.33	∞		−19.88	
1b	NO_2	R	−93.40	∞	1.62			
		TS1	−60.70	1.85	1.67	32.70		599.6i
		2b	−78.71	1.41	189	14.69	0	
		TS2	−77.92	1.39	1.93		0.81	130.4i
		P	−98.40	1.33	∞		−19.69	
1c	NH_2	R	−97.20	∞	1.61	0		
		TS1	−65.10	1.82	1.67	32.10		599.6i
		2c	−78.96	1.40	1.89	18.24	0	
		TS2	−78.76	1.35	1.96		0.20	212.5i
		P	−98.46	1.33	∞		−19.50	

[a] R and P are the reactants and products respectively; structure (**2**) is the intermediate and **TS1** and **TS2** are the transition states on the reactant and product sides of the reaction respectively. [b] Heat of formation (kcal mol^{-1}). [c] Bond lengths (Å). [d] δE_1 And δE_2 are the energy differences calculated from the reactants and intermediate respectively (both kcal mol^{-1}). [e] Wavenumbers (cm^{-1}).

This initial transition state (**TS1**) is reactant-like in each case studied with the NC–SAr bond stretched to 1.67 Å from 1.61–1.62 Å in the phenylthiocyanates alone with the MeO–CN distance ranging from 1.82 to 1.85 Å depending on the ring substituent (Table 3). In the intermediates (**2a–c**), the NC–SAr and MeO–CN bond lengths at *ca.* 1.89 and 1.40 Å, respectively, are somewhat longer than those found either in the phenylthiocyanate alone at 1.61 Å or in methylcyanate at around 1.33 Å (Table 3). The negative charge on the intermediates, is distributed mainly over the cyano nitrogen atom, N9, the sulfur atom, S7, and the attached oxygen atom. The positive charge at the sulfur atom of phenylthiocyanate itself in methanol therefore, changes from 0.566 to −0.176 in the intermediate, and the negative charge at the nitrogen atom increases from −0.121 to −0.643 in line with the structural representation (**2**) shown (Scheme 1).

As the methoxide ion is moved closer to the cyano carbon of the phenylthiocyanates to form the products, there is a slight increase in energy only to give a second transition state (**TS2**) which is located between the intermediate (**2**) and the product combination of methylcyanate and the phenylthiolate ion (Scheme 1). Thermodynamically, this process is predicted to be exothermic in each case but there is no pronounced substituent effect (Table 3). The activation energy of this displacement process is much smaller than the addition reaction, and the transition states (characterised by their single imaginary vibrational frequency in each case) are predicted to be less than 1 kcal mol^{-1} above the respective intermediate (Table 3, Fig. 2). This second transition state (TS2) is product-like in each case with NC–OMe bond lengths of around 1.35–1.39 Å *vs.* 1.33 Å in methylcyanate and with ArS–CN distances ranging from 1.93 to 1.96 Å (Table 3).

Overall, the rate controlling step of this nucleophilic substitution reaction is the addition of methoxide ion to the cyano group to give a high energy intermediate (**2**); ring substituents do not appear to greatly influence this process. Thermodynamically, however, the substituents do exert an effect and the driving force for the reaction to form methylcyanate and the arylthiolate ion is greatest for the 4-nitro derivative (**1b**) and least for the 4-amino derivative (**1c**) with values of −5.00 and −1.26 kcal mol^{-1} *vs.* −3.19 kcal mol^{-1} for phenylthiocyanate itself (**1a**) (Table 3, Fig. 2).

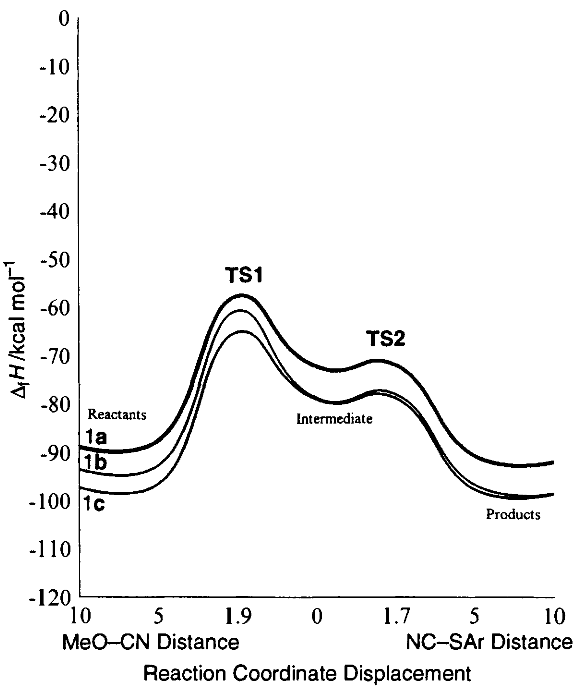
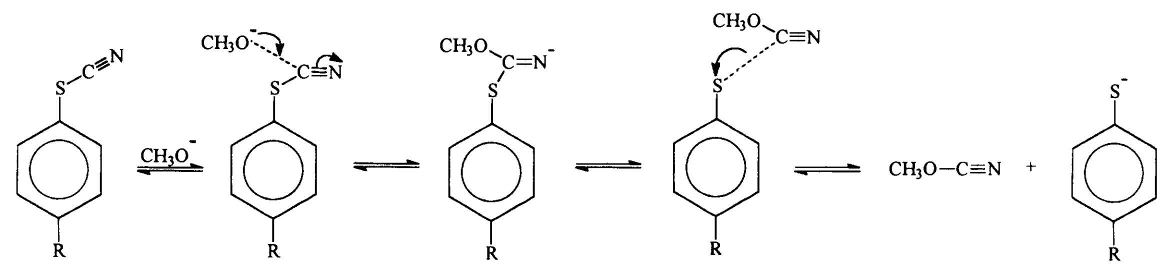


Fig. 2 Energetics of the reaction of methoxide ion at the cyano carbon of the phenylthiocyanates in methanol along the reaction coordinate [distances are given from those found in the intermediate (**3**)]

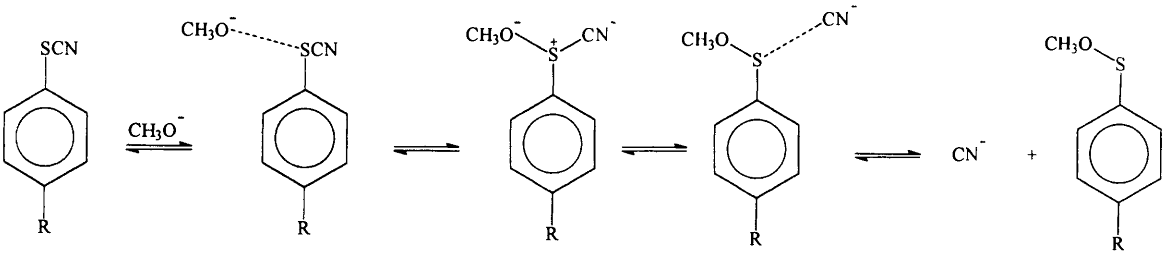
2.2 Attack at the sulfur atom (Scheme 2). The corresponding nucleophilic attack by methoxide ion at the sulfur atom, S7, (Scheme 2) is predicted to result in the formation of a stable intermediate (**3**), which is approximately equal to or lower in energy than the reactants. We have found a similar stable intermediate in the related reaction of phenylthiocyanate (**1a**) with methane thiolate using the AM1-SM1 method.[11] In this work, the 4-nitrophenylthiocyanate intermediate (**3b**) is thermodynamically favoured over the parent (**3a**) which in turn is favoured over the 4-amino derivative (**3c**) with values relative to the reactants of −2.97, 0.05 and 1.17 kcal mol^{-1}, respectively (Table 4). In the charged intermediate depicted as the approximate valence bond structure (**3a**), the sulfur atom has a large positive charge of 0.601 *vs.* 0.566 on the same atom in phenylthiocyanate itself, which is stabilised by the surrounding negative charges of −0.602 at the methoxy group, −0.661 at the cyano group and −0.342 found at the aromatic ring.

A similar order of substituent trends is found for the activation energies of the attack at sulfur with the barrier greatest for 4-aminophenylthiocyanate (**1c**) and least for the



1 **TS1** **2** **TS2**

Scheme 1 Proposed reaction path for the attack of methoxide ion at the cyano carbon of the phenylthiocyanates (**1a–c**) in methanol



1 **TS1** **3** **TS2**

Scheme 2 Proposed reaction path for the attack of methoxide ion at the sulfur atom of the phenylthiocyanates (**1a–c**) in methanol

Table 4 Enthalpies of the reactions of phenylthiocyanates (**1**) with methoxide ion in methanol at the sulfur atom, transition state geometries and reaction coordinate vibrational frequencies, calculated using the AM1/COSMO method

	R^1	Coordinate position[a]	$\Delta_f H$[b]	TS geometry[c] MeO–S	S–CN	Relative energy[d] δE_1	δE_2	Frequency[e]
1a	H	R	−88.83	∞	1.60			
		TS1	−74.05	2.49	1.62	14.83		144.2i
		3a	−88.78	1.82	1.68	0.05	0	
		TS2	−63.61	1.71	3.01		25.17	117.7i
		P	−69.53	1.70	∞		19.25	
1b	NO_2	R	−93.40	∞	1.61			
		TS1	−80.85	2.50	1.62	12.82		191.4i
		3b	−96.37	1.81	1.67	−2.97	0	
		TS2	−67.50	1.71	2.95		28.87	195.6i
		P	−74.84	1.70	∞		21.53	
1c	NH_2	R	−97.20	∞	1.60			
		TS1	−81.50	2.57	1.61	15.70		527.8i
		3c	−95.43	1.82	1.68	1.77	0	
		TS2	−70.79	1.71	3.01		24.64	104.0i
		P	−76.50	1.70	∞		18.93	

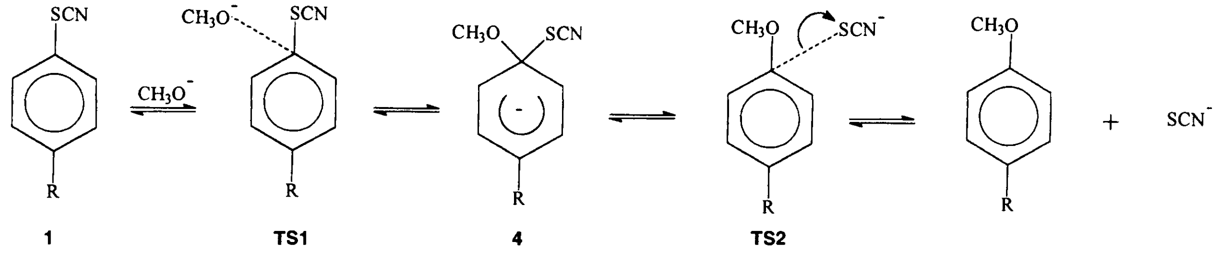
[a] R And P are the reactants and products respectively; structure (**3**) is the intermediate and **TS1** and **TS2** are the transition states on the reactant and product sides of the reaction respectively. [b] Heat of formation (kcal mol^{-1}). [c] Bond lengths (Å). [d] δE_1 And δE_2 are the energy differences calculated from the reactants and intermediate respectively (both kcal mol^{-1}). [e] Wavenumbers (cm^{-1}).

4-nitro derivative (**1b**) with values of 15.7 and 12.8 kcal mol^{-1}, respectively, *vs.* 14.8 kcal mol^{-1} for the parent (Table 4, Fig. 3).

The initial transition state of this reaction (**TS1**) is reactant-like as in the previous case with the MeO–S distance *ca.* 2.5 Å and with a corresponding S–CN bond length of 1.62 Å from *ca.* 1.60 Å in the phenylthiocyanates alone (Table 4). In all the intermediates (**3a–c**), the MeO–S and S–CN bond lengths are now significantly shorter at 1.81–1.82 Å and longer at 1.67–1.68 Å, respectively, than those found in the transition state (Table 4).

In contrast to the attack at the cyano carbon, as the methoxide ion is moved closer to the sulfur atom of the phenylthiocyanates to form the products (Scheme 2), there is a large increase in energy to give a second transition state (**TS2**) which is located between the intermediate (**3**) and the products (Fig. 3). This transition state (**TS2**) is much higher in energy than that encountered (**TS1**) during the formation of the intermediate (**3**). In contrast to previous trends, the transition state (**TS2**) for the 4-amino derivative (**1c**) is favoured over those for the parent (**1a**) and the 4-nitro derivative (**1b**) with values of 24.6, 25.2 and 28.9 kcal mol^{-1} above the corresponding stable intermediate (**3**), respectively, (Table 4, Fig. 3). This second transition state (**TS2**) is product-like in each case with MeO–S bond lengths of 1.71 Å and S–CN distances ranging from 2.95 to 3.01 Å (Table 4). Thermodynamically, the nucleophilic displacement process is predicted to be endothermic in each case with the 4-amino derivative (**1c**) again surprisingly favoured by a small margin over the others (**1a**) and (**1b**) with values of 18.9, 19.3 and 21.5 kcal mol^{-1}, respectively, (Table 4).

Unlike the previous case, therefore, the rate controlling step of the overall nucleophilic substitution reaction at sulfur is clearly the displacement of the cyanide ion from the stable intermediate (**3**). While it is not entirely clear why the displacement appears kinetically to be more facile for 4-aminophenylthiocyanate (**1c**) than that for 4-nitrophenylthiocyanate (**1b**), given the stabilising effect of the nitro group which



Scheme 3 Proposed reaction path for the attack of methoxide ion at the aryl carbon atom of the phenylthiocyanates (**1a–c**) in methanol

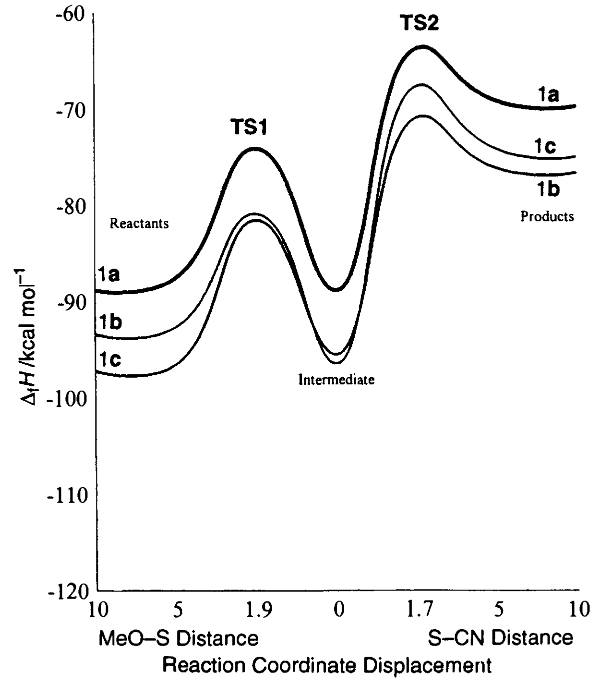


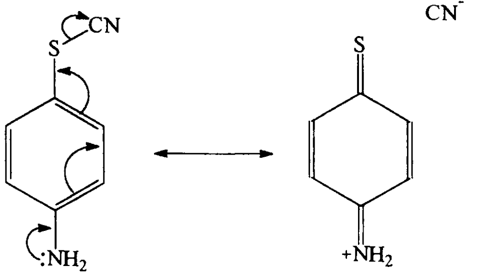
Fig. 3 Energetics of the reaction of methoxide ion at the sulfur atom of the phenylthiocyanates in methanol along the reaction coordinate [distances are given from those found in the intermediate (**3**)]

increases the positive charge at the sulfur atom of the substrate from 0.492 to 0.577 (Table 2), one contributory factor is likely to arise from a mechanism where the amino group facilitates the expulsion of the cyanide ion *via* a charge separated canonical form (Scheme 4).

Thermodynamically, however, the overall process is endothermic with the 4-nitro derivative (**1b**) favoured over the parent (**1a**) which in turn is preferred over the 4-amino derivative (**1c**) with values of 18.6, 19.3 and 20.7 kcal mol^{-1}, respectively, (Table 4).

2.3 Attack at the aryl carbon (Scheme 3). In terms of the mechanism of the nucleophilic displacement process at the aryl carbon of the phenylthiocyanates, C1, (eqn. 3), the reaction of the 4-nitro derivative (**1b**) is predicted to proceed *via* a stable Meisenheimer type complex or intermediate (**4b**) which has two distinct saddle points or transition states (Scheme 3, Fig. 4) in line with experimental data for this type of reaction.[8,9] The first step of the process involving the addition of the nucleophile to the aromatic ring of the 4-nitro derivative (**1b**) is predicted to be the highest energy point along the reaction coordinate with a barrier of 32.0 kcal mol^{-1} between reactants and intermediate (**4b**). Thermodynamically, the formation of intermediate (**4b**) is a slightly endothermic process but by only 0.20 kcal mol^{-1} (Table 5).

The second transition state (**TS2**) between the intermediate (**4b**) and the product combination of 4-nitroanisole and the thiocyanate ion (Scheme 3) is very close to the intermediate with a barrier height of only 0.30 kcal mol^{-1} (Table 5, Fig. 4): the rate determining step of the nucleophilic process is thus the addition of methoxide ion to the ring in a similar way to the related addition of methoxide ion to ethyl picrate.[8,9] The initial transition state (**TS1**) is clearly reactant-like as in the previous cases with a fairly long MeO–Ar distance of 1.99 Å and a Ar–SCN distance of 1.75 Å *vs.* 1.69 Å in the reactant (**1b**). The second transition state (**TS2**) is product-like with the Ar–SCN distance now at 1.98 Å and the MeO–Ar distance at 1.41 Å close to that found in the product, 4-nitroanisole, at 1.37 Å (Table 5).



Scheme 4 Charge separated canonical form of 4-aminophenylthiocyanate

In the intermediate (**4b**), the MeO–Ar and Ar–SCN bonds lengths at 1.42 and 1.95 Å are significantly longer than the corresponding bonds found in 4-nitroanisole at 1.37 Å or 4-nitrophenylthiocyanate at 1.69 Å, respectively. The negative charge on the intermediate (**4b**) is not only accommodated by the aromatic ring at the *ortho* and *para* positions with values of −0.288 (C2), −0.353 (C4) and −0.298 (C6), but also by the positively charged sulfur atom which shows a reduction in charge from 0.621 in the reactant (**1b**) to 0.168 in the intermediate (**4b**).

No intermediate could be found for the reaction of methoxide ion at the aryl carbon of either phenylthiocyanate (**1a**) or the 4-amino derivative (**1c**). These reactions are predicted to proceed to the product mixture of the anisole and thiocyanate ion *via* a single transition state (**TS1**) only (Fig. 4). Repeated attempts to generate an intermediate either from the saddle calculation or from intermediate (**4b**) by removing the substituent and carefully adjusting the bond lengths failed, and the structure always collapsed into the products on optimisation. A comparison of the activation energies of the nucleophillic addition show that the 4-nitro derivative (**1b**) is favoured by a substantial margin over the 4-amino derivative (**1c**) with values of 32.0 and 47.2 kcal mol^{-1}, respectively, with the parent lying approximately mid way between the two extremes at 40.8 kcal mol^{-1} (Table 5).

As far as the thermodynamics of this process is concerned, the substitution is strongly exothermic with the 4-nitro derivative (**1b**) showing the largest energy difference between reactants and products, the 4-amino derivative (**1c**) the least, with the parent (**1a**) again lying between with values of −27.6, −22.9 and −25.3 kcal mol^{-1}, respectively (Table 5).

Conclusions

In terms of overall stability, nucleophilic attack by methoxide ion at the aryl carbon with the displacement of the thiocyanate anion (Scheme 3, Fig. 4) is much the preferred process in all three cases by around −23.0 to −27.4 kcal mol^{-1}, followed by

Table 5 Enthalpies of the reactions of phenylthiocyanates (**1**) with methoxide ion in methanol at the aryl group, transition state geometries and reaction coordinate vibrational frequencies, calculated using the AM1/COSMO method

				TS geometry[c]		Relative energy[d]		
	R^1	Coordinate position[a]	$\Delta_f H$[b]	MeO–Ar	Ar–SCN	δE_1	δE_2	Frequency[e]
1a	H	R	−88.83	∞	1.70	0		
		TS1	−48.02	1.81	1.78	40.81		610.6i
		P	−114.1	1.38	∞		−25.27	
1b	NO_2	R	−93.40	∞	1.69	0		
		TS1	−61.41	1.99	1.75	31.99		551.7i
		4b	−93.20	1.42	1.95	0.20	0	
		TS2	−93.17	1.41	1.98		0.30	153.4i
		P	−120.8	1.37	∞		−27.60	
1c	NH_2	R	−97.20	∞	1.69	47.23		652.83i
		TS1	−49.97	1.88	1.79			
		P	−120.1	1.38	∞		−22.92	

[a] R and P are the reactants and products respectively; structure (**4**) is the intermediate and **TS1** and **TS2** are the transition states on the reactant and product sides of the reaction respectively. [b] Heat of formation (kcal mol^{-1}). [c] Bond lengths (Å). [d] δE_1 And δE_2 are the energy differences calculated from the reactants and intermediate respectively (both kcal mol^{-1}). [e] Wavenumbers (cm^{-1}).

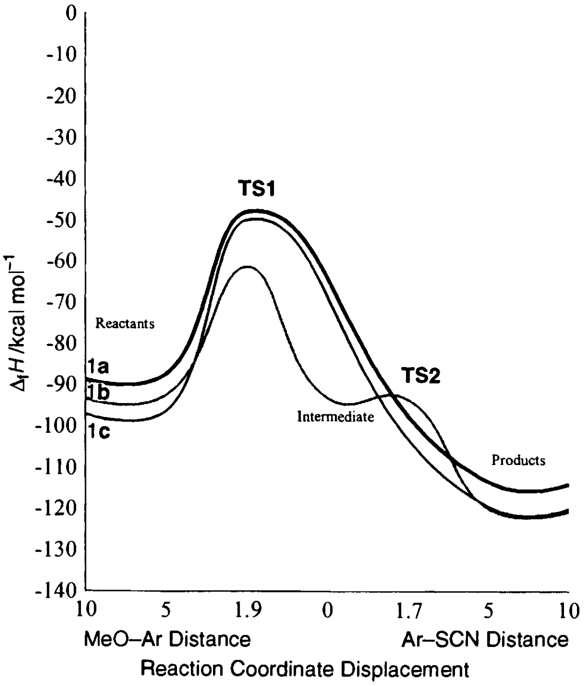


Fig. 4 Energetics of the reaction of methoxide ion at the aryl carbon atom of the phenylthiocyanates in methanol along the reaction coordinate [distances are given from those found in the intermediate (3)]

the alternative attack at the cyano carbon resulting in the displacement of the phenylthiolate anion (Scheme 1, Fig. 2) with energies here ranging from −1.26 to −5.00 kcal mol^{-1}. The corresponding attack at the sulfur atom with the displacement of the cyanide ion (Scheme 2, Fig. 3) is strongly disfavoured with energies here ranging from 18.5 to 20.7 kcal mol^{-1}. The thermodynamic trends found for the two favourable reactions, match those expected on the basis of the known electronic character of the substituents,[8,9] with the nitro group facilitating both displacement reactions by stabilising the negative charge of the incoming nucleophile by electron attraction, and the amino group retarding the displacement reaction by classical electron donation into the aromatic ring.

In terms of the kinetics of the attack of the methoxide ion at the three possible electrophilic centres of the phenylthiocyanates, the reaction selectivity is highly dependent on the substituent present. All three molecules readily form reversible complexes at the sulfur atom. The barrier heights for 4-nitrophenylthiocyanate (**1b**) are predicted to be approximately equal for the attack at either the aryl carbon or cyano carbon with values of 32.0 and 32.7 kcal mol^{-1}, respectively, and the trends predicted by the AM1/COSMO method are broadly consistent with the expected experimental reactivity. In contrast, the barrier heights for phenylthiocyanate (**1a**) and 4-aminophenylthiocyanate (**1c**) are smallest for the attack at the cyano carbon with values of 31.2 and 32.1 kcal mol^{-1} *vs.* 40.8 and 47.2 kcal mol^{-1} for the corresponding attack at the aryl carbon. The trends in selectivity predicted by the molecular orbital method again appear to match those expected on the basis of the known experimental reactivities of phenylthiocyanate with other nucleophiles.

References

1 *The Chemistry of Cyanates and Their Thio Derivatives*, ed. S. Patai, Wiley, New York, 1977.
2 D. E. Giles and A. J. Parker, *Aust. J. Chem.*, 1973, **26**, 273.
3 J. Miller and F. H. Kendall, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1645.
4 J. H. Keen, W. H. Habig and W. B. Jakby, *J. Biol. Chem.*, 1976, **251**, 6183.
5 Y. Degani, H. Neumann and A. Patchornik, *J. Am. Chem. Soc.*, 1970, **92**, 6969.
6 Y. Degani and A. Patchornik, *Biochemistry*, 1974, **13**, 1.
7 T. Austad and S. Esperas, *Acta Chem. Scand.*, 1976, **3**, 563.
8 E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, Inc., New York, 1964.
9 J. March, Advanced Organic Chemistry, Wiley, New York, 1985.
10 See for example: W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, Ab Initio *Molecular Orbital Theory*, Wiley, New York, 1986, pp. 360–370.
11 J. O. Morley and M. Naji, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1301.
12 J. O. Morley, *Int. J. Quantum Chem.*, in the press.
13 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
14 J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 209.
15 MOPAC 93, J. J. P. Stewart and Fujitsu Limited, Tokyo, Japan, copyright (Fujitsu Limited, 1993) obtained from QCPE, Department of Chemistry, Indiania University, Bloomington, Indiana 47405, USA.
16 A. Klamt and G. Schuurmann, *J. Chem. Soc., Perkin Trans. 2*, 1993, 799.
17 Cambridge Structural Database, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 2EW.
18 I. V. Isakov, E. E. Rider and Z. V. Zvonkova, *Kristallografiya*, 1977, **22**, 1086.

19 S. Millefiori and A. Foffani, *Tetrahedron*, 1966, **22**, 803.

20 E. Bergmann, L. Engel and H. A. Wolff, *Z. Physik. Chem.*, 1930, **B120**, 397.

21 A. E. Lutskii, E. M. Obukhova, L. M. Yagupol'skii and V. G. Voloshchuk, *J. Struct. Chem.*, 1969, **10**, 326.

22 T. W. Campbell and M. T. Rodgers, *J. Am. Chem. Soc.*, 1948, **70**, 1029.

Paper 5/07065A
Received 26*th October* 1995
Accepted 1*st December* 1995