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Enforced slow protonation of $[Fe_4S_4Cl_4]^{2-}$ and the maximum rate of protonation of the cluster core †

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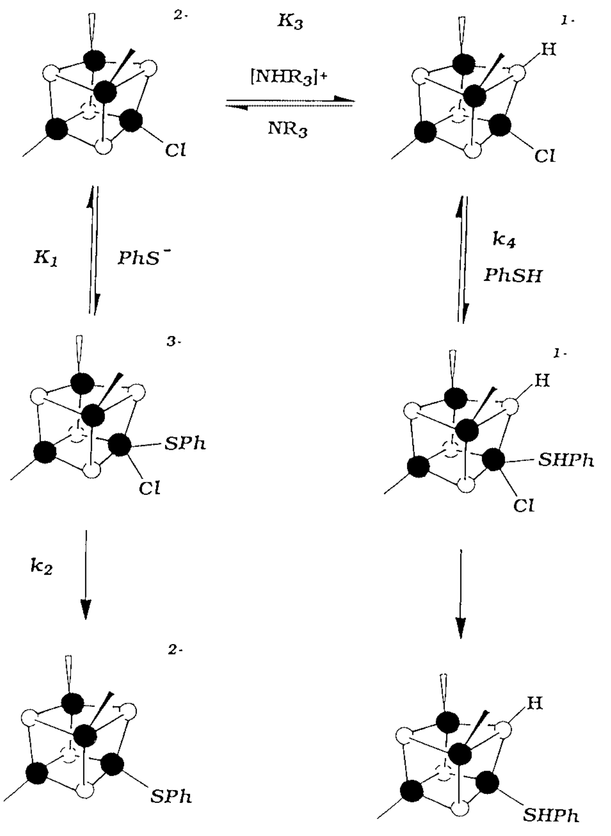
Kinetic studies on the reaction of PhS^- with $[Fe_4S_4Cl_4]^{2-}$ ($pK_a = 18.8$) in the presence of the weak acid $[\overline{NH_2(CH_2)_3CH_2}]^+$ in MeCN showed that the mechanism involves initial, rate-limiting, binding of PhS^- to the cluster, followed by protonation of the cluster core (presumably a μ_3-S), then dissociation of chloride. This is different to the sequence of elementary reactions established with the stronger acid, $[NHEt_3]^+$ ($pK_a = 18.5$), where protonation precedes binding of the thiol. Quantitative comparison of these two systems reveals that the literature value of $pK_a = 19.6$ for $[\overline{NH_2(CH_2)_3CH_2}]^+$ is inconsistent with our kinetic results and that $pK_a = 21.5$ is more appropriate, both in this and other systems. The kinetic data show that the rate of protonation of the cluster core falls in the range $2 \times 10^5 \le k \le 4.8 \times 10^6$ dm^3 mol^{-1} s^{-1}, for a thermodynamically favourable reaction. The reasons why this protonation is 10^4–10^5 times slower than the diffusion-controlled limit are discussed.

Introduction

Iron–sulfur-based clusters are found in many proteins, where they primarily fulfil the roles of electron-transfer agents and substrate binding sites in redox and non-redox catalysis.[1] In the laboratory, synthetic iron–sulfur-based clusters now constitute a large family of structurally related compounds, some of which are models for these biological centres.[2,3] Studies on the synthetic clusters allow us to establish the characteristic reactivity patterns of this family of compounds, and hence the intrinsic reactivity of the biological sites unaffected by interactions with the engulfing polypeptide. One of the most fundamental reactions of iron–sulfur-based clusters is their ability to bind protons and it is one aspect of this problem that we address in this paper.

Previously[4,5] we have shown how the protonation chemistry of synthetic and naturally occurring Fe–S-based clusters can be established indirectly, by monitoring the effect that acid has on the rate of substitution, in MeCN as solvent. The two most general features are:[5] (i) single protonation of the cluster core is labilising and (ii) this protonation is associated with $pK_a = 18.5 \pm 0.5$, essentially independent of the geometry of the cluster and the identity of the terminal ligands. The studies to date have used the relatively strong acids $[NHEt_3]^+$ ($pK_a = 18.4$)[6] and $[Hlut]^+$ (lut = 2,6-dimethylpyridine, $pK_a = 15.4$)[7] so that the protonation of the clusters is thermoneutral or exoergic. These reactions are true acid-catalysed substitution processes (Scheme 1), with protonation rapidly preceding binding of the nucleophile (in associative substitution mechanisms), and rate-limiting dissociation of the leaving group.

Studies on $[Fe_4S_4Cl_4]^{2-}$ have the advantage that the protonation must be at the cluster core (presumably a μ_3-S) since the chloro-ligands are insufficiently basic to be protonated by the acids used.[8] Protonation of this cluster by $[NHEt_3]^+$ or $[Hlut]^+$ is never rate-limiting and consequently only a lower limit of the rate constant for protonation of the core can be estimated ($k_3 \ge 2 \times 10^5$ dm^3 mol^{-1} s^{-1}). In this paper we focus further on the act of protonation. We now report the kinetics of the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^-, eqn. (1), in the presence of $[\overline{NH_2(CH_2)_3CH_2}]^+$. With this acid protonation of the cluster is thermodynamically unfavourable and consequently is slow.



Scheme 1 Substitution pathways for the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^- in the absence (left hand side, dissociative pathway, k_0 is not shown) and presence (right hand side) of $[NHEt_3]^+$ in MeCN. For simplicity, only one chloro-ligand is shown.

$$[Fe_4S_4Cl_4]^{2-} + PhS^- \longrightarrow [Fe_4S_4(SPh)Cl_3]^{2-} + Cl^- \quad (1)$$

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† *Supplementary data available*: observed rate constants. For direct electronic access see http://www.rsc.org/suppdata/dt/1999/3927/, otherwise available from BLDSC (No. SUP 57666, 5 pp.) or the RSC Library. See Instructions for Authors, 1999, Issue 1 (http://www.rsc.org/dalton).

From the data reported herein we can show, for the first time, that the rate of protonation of the cluster core is 10^4–10^5 times slower than the diffusion-controlled limit even for thermodynamically favourable protonation reactions.

Experimental

All manipulations were routinely performed under an atmosphere of dinitrogen using Schlenk and syringe techniques as appropriate. The compounds $[\mathrm{NBu^n_4}]_2[\mathrm{Fe_4S_4Cl_4}]$,[9] $[\mathrm{NMe_4}]_2[\mathrm{Fe_4S_4(SEt)_4}]$[10] and $[\mathrm{NEt_4}][\mathrm{SPh}]$[11] were prepared by the literature methods; $\overline{\mathrm{NH(CH_2)_3C}}\mathrm{H_2}$ (Aldrich) stored over KOH pellets and distilled immediately prior to use and PhSH (Aldrich) used as received.

All solvents were stored and dried over the appropriate drying agent and distilled immediately prior to use: MeCN ($\mathrm{CaH_2}$); tetrahydrofuran (sodium–benzophenone) and MeOH (NaOMe).

Preparation of $[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}][\mathrm{BPh_4}]$

This material was prepared by a method analogous to that described[12] for $[\mathrm{NHEt_3}][\mathrm{BPh_4}]$. To a solution of $\overline{\mathrm{NH(CH_2)_3C}}\mathrm{H_2}$ (3.5 g; 49 mmol) in tetrahydrofuran was added $\mathrm{SiMe_3Cl}$ (5.5 ml; 50 mmol) then MeOH (1.6 ml; 50 mmol). The white precipitate of $[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}]\mathrm{Cl}$ was stirred for *ca.* 30 min, filtered, washed with tetrahydrofuran then dried *in vacuo*.

The dry solid was dissolved in the minimum volume of MeOH, filtered through Celite to remove a fine suspension, then an equimolar amount of $\mathrm{NaBPh_4}$ in MeOH (also filtered through Celite) was added dropwise to give white crystals. After standing overnight the solid was filtered in air, washed with large volumes of distilled water (to remove NaCl), then MeOH and finally dried in air (yield *ca.* 70%). The compound $[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}][\mathrm{BPh_4}]$ was characterised by elemental analysis and ^{1}H NMR spectroscopy. Found (calculated): C 86.0 (85.9); H 7.6 (7.7); N 3.6 (3.6%). ^{1}H NMR: 2.12 (multiplet; $\mathrm{NCH_2}$-$\mathrm{C}H_2$); 3.22 (triplet, $J_{\mathrm{HH}} = 7.5$ Hz; $\mathrm{N}CH_2\mathrm{CH_2}$); 6.14 (broad; $\mathrm{N}H_2\mathrm{CH_2}$) and 7.37–7.88 (three multiplets, $\mathrm{BPh_4}$).

Stopped-flow studies

All solutions were prepared under an atmosphere of dinitrogen and transferred by gas-tight, all-glass syringes into the stopped-flow spectrophotometer. Solutions of various mixtures of $[\mathrm{NEt_4}][\mathrm{SPh}]$, PhSH, $\overline{\mathrm{NH(CH_2)_3C}}\mathrm{H_2}$ and $[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}][\mathrm{BPh_4}]$ were prepared from freshly prepared stock solutions of the reagents, and used within 1 h. The ionic strength of all solutions was maintained at 0.1 mol dm^{-3} using $[\mathrm{NBu^n_4}][\mathrm{BF_4}]$.

All kinetic studies were performed on a Hi-Tech Scientific SF-51 stopped-flow spectrophotometer, modified to handle air-sensitive solutions.[13] The temperature was maintained at 25.0 °C using a Grant LE8 thermostat tank. The data were collected, stored and analysed on a Viglen computer, connected to the stopped-flow machine *via* an analogue-to-digital converter.

All kinetics were studied under pseudo first-order conditions with all reagents in a large excess (>10-fold) over the concentration of cluster. In all cases the absorbance–time curve was measured at $\lambda = 560$ nm, and had an initial absorbance which corresponds to that of $[\mathrm{Fe_4S_4Cl_4}]^{2-}$ whilst the final absorbance was that of $[\mathrm{Fe_4S_4(SPh)_4}]^{2-}$. This curve thus corresponds to complete substitution of all four terminal chloro-ligands as shown in eqn. (2).

$$[\mathrm{Fe_4S_4Cl_4}]^{2-} + 4\mathrm{PhS}^- \xrightarrow{[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}]^+} [\mathrm{Fe_4S_4(SPh)_4}]^{2-} + 4\mathrm{Cl}^- \quad (2)$$

The entire curve could be fitted by two exponentials of equal magnitude using a computer curve-fitting program. For simplicity we are interested in the first act of substitution corresponding to eqn. (1), and thus all the data discussed in this paper are associated with the first (faster) exponential. The second exponential curve responds to changes in the concentrations of the various reagents in a parallel fashion to that of the first exponential curve.

The exponential nature of these curves indicates a first order dependence on the concentration of the cluster.[14] This was confirmed, under all conditions, by studies in which the concentration of cluster was varied while the concentrations of all the other reagents were kept constant. In all cases the observed rate constant (k_{obs}) did not vary more than ±3%. The rate constants for both stages observed under all conditions reported herein are presented in the supplementary data (SUP 57666).

The dependence of the reaction rate on the concentrations of $[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}]^+$, $\overline{\mathrm{NH(CH_2)_3C}}\mathrm{H_2}$, $\mathrm{PhS^-}$ or PhSH was established by conventional graphical methods, as shown in the Results and discussion section.

Results and discussion

The discussion that follows will present our findings in the following order. (1) Description of the kinetics for the reaction between $[\mathrm{Fe_4S_4Cl_4}]^{2-}$ and $\mathrm{PhS^-}$ in the presence of $[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}]^+$, and comparison with the earlier studies using $[\mathrm{NHEt_3}]^+$. (2) Discussion of the pK_a of $[\overline{\mathrm{NH_2(CH_2)_3C}}\mathrm{H_2}]^+$ in the literature and that estimated from our kinetic results. (3) Analysis of the kinetic data to show that the rate of protonation of the cluster core falls in the range, $2 \times 10^5 \le k_3 \le 4.8 \times 10^6$ dm^3 mol^{-1} s^{-1} and discussion of why this value is 10^4–10^5 times slower than the diffusion-controlled limit.

Before presenting the new results it is important to put this work into context. In particular to appreciate the markedly different kinetic behaviour observed in the present study to that previously reported in the presence of $[\mathrm{NHEt_3}]^+$. Consequently, the salient features of the $[\mathrm{NHEt_3}]^+$ system will be described in the next section.[8]

Substitution kinetics in the presence of $[\mathrm{NHEt_3}]^+$

The mechanism of the reaction between $[\mathrm{Fe_4S_4Cl_4}]^{2-}$ and $\mathrm{PhS^-}$ in MeCN occurs predominantly by the associative pathway shown on the left hand side of Scheme 1. The effect of $[\mathrm{NHEt_3}]^+$ on the rate of this reaction is complicated.[8] At low concentrations of acid ($[\mathrm{NHEt_3}^+] \le [\mathrm{PhS^-}]$), the rate progressively decreases as the concentration of acid is increased. This corresponds to the stoichiometric conversion of $\mathrm{PhS^-}$ into PhSH (*i.e.* effective removal of $\mathrm{PhS^-}$ and replacement by the poorer nucleophile PhSH). Consequently the rate is a minimum when $[\mathrm{NHEt_3}^+] = [\mathrm{PhS^-}]$. Further increase in the concentration of acid ($[\mathrm{NHEt_3}^+] > [\mathrm{PhS^-}]$) results in an increase in the rate as now the $[\mathrm{NHEt_3}]^+$ present protonates the cluster, and the substitution pathway is that shown on the right hand side of Scheme 1.

Quantitative analysis of this behaviour is relatively straightforward since in the presence of an excess of $[\mathrm{NHEt_3}]^+$ the protolytic equilibrium (3) lies to the right hand side and the concentrations of the various components are given by the simple expressions (4)–(6). Here, and for the remainder of this paper, the subscript ‘0’ designates the concentration of the reagent added to the solution, whilst ‘e’ indicates the concentration at equilibrium.

$$[\mathrm{NHEt_3}]^+ + \mathrm{PhS}^- \overset{K_\mathrm{A}}{\rightleftharpoons} \mathrm{NEt_3} + \mathrm{PhSH} \quad (3)$$

$$[\mathrm{NHEt_3}^+]_\mathrm{e} = [\mathrm{NHEt_3}^+]_0 - [\mathrm{PhS^-}]_0 \quad (4)$$

$$[\mathrm{NEt_3}]_\mathrm{e} = [\mathrm{NEt_3}]_0 + [\mathrm{PhS^-}]_0 \quad (5)$$

$$[\mathrm{PhSH}]_\mathrm{e} = [\mathrm{PhSH}]_0 + [\mathrm{PhS^-}]_0 \quad (6)$$

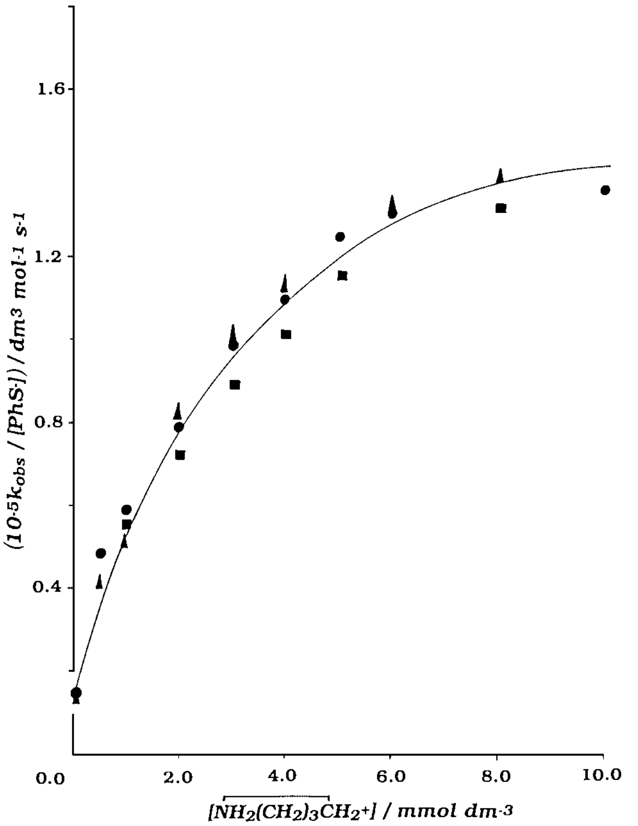


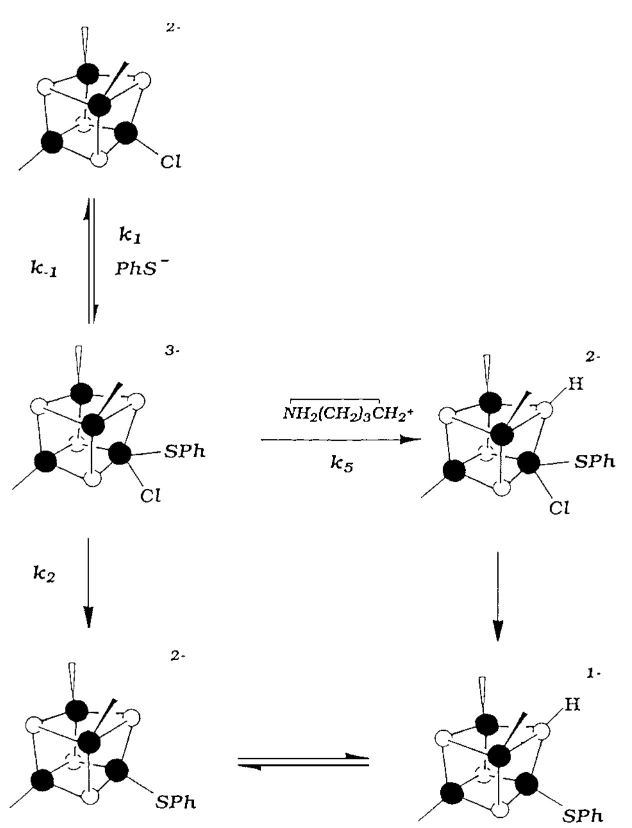
Fig. 1 Dependence of $k_{obs}/[\mathrm{PhS^-}]$ on the concentration of $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}]^+$ for the reaction between $[\mathrm{Fe_4S_4Cl_4}]^{2-}$ and $\mathrm{PhS^-}$ in MeCN at 25.0 °C {ionic strength = 0.1 mol dm^{-3} ($[\mathrm{NBu^n_4}][\mathrm{BF_4}]$}; $[\mathrm{Fe_4S_4Cl_4}^{2-}] = 0.05$ mmol dm^{-3}. Data points correspond to: $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}^+] = 0$–$10$ mmol dm^{-3}, $[\mathrm{PhS^-}] = 1.0$ mmol dm^{-3} (■); $[\mathrm{PhS^-}] = 0.5$ mmol dm^{-3} (●); $[\mathrm{PhS^-}] = 0.25$ mmol dm^{-3} (▲). Curve drawn is that defined by eqn. (8).

Systematic variation of $[\mathrm{NHEt_3}^+]_e$, $[\mathrm{NEt_3}]_e$ and $[\mathrm{PhSH}]_e$ showed that the kinetics of the reaction are described by eqn. (7).[8] The numerator contains three terms, corresponding to

$$\frac{-\mathrm{d}[\mathrm{Fe_4S_4Cl_4}^{2-}]}{\mathrm{d}t} = \left\{\frac{k_0 + k_2K_1[\mathrm{PhS^-}]_e}{1 + K_1[\mathrm{PhS^-}]_e} + \frac{(K_3k_4[\mathrm{NHEt_3}^+]_e/[\mathrm{NEt_3}^+]_e)[\mathrm{PhSH}]_e}{1 + (K_3[\mathrm{NHEt_3}^+]_e/[\mathrm{NEt_3}]_e)}\right\}[\mathrm{Fe_4S_4Cl_4}]^{2-} \quad (7)$$

three pathways for substitution at various acid concentrations. The first term describes the dissociative substitution pathway of $[\mathrm{Fe_4S_4Cl_4}]^{2-}$ ($k_0 = 2.0$ s^{-1}), and the second the associative substitution pathway in the absence of acid ($k_2 = 2.5 \times 10^2$ s^{-1} and $K_1 = 68.4$ dm^3 mol^{-1}). The third term describes the acid-catalysed pathway in the presence of $[\mathrm{NHEt_3}^+]$ ($K_3 = 2.2$ and $k_4 = 1.5 \times 10^4$ dm^3 mol^{-1} s^{-1}). Of particular note is the denominator for this term which depends only on $[\mathrm{NHEt_3}^+]_e/[\mathrm{NEt_3}]_e$. The absence of a dependence on $[\mathrm{PhSH}]_e$ in the denominator dictates a mechanism in which protonation of the cluster is rapid and precedes binding of the PhSH and dissociation of the chloride.

Substitution kinetics in the presence of $[\mathrm{H_2\overline{N(CH_2)_3CH_2}}]^+$



Scheme 2 Mechanism for the reaction between $[\mathrm{Fe_4S_4Cl_4}]^{2-}$ and $\mathrm{PhS^-}$ in the presence of $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}]^+$ in MeCN.

The effect of $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}]^+$ on the kinetics of eqn. (1) is shown in Fig. 1, and is clearly different to that described above for $[\mathrm{NHEt_3}]^+$. In particular, the following features distinguish the two systems. (i) The rate does not reach a minimum when $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}^+]_0 = [\mathrm{PhS^-}]_0$, but shows a uniform, non-linear increase in the rate throughout the range of acid concentration used. (ii) The addition of $\mathrm{\overline{NH(CH_2)_3CH_2}}$ does not affect the kinetics (see below). (iii) At constant $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}^+]_0$, the rate varies linearly with the concentration of $\mathrm{PhS^-}$ at all concentrations of $\mathrm{PhS^-}$ and (iv) independent studies show that the reaction is *ca.* 15 times slower if $\mathrm{PhS^-}$ is replaced by PhSH (see below).

Analysis of the data in Fig. 1 gives the experimental rate law (8). This equation is consistent with the mechanism shown in

$$\frac{-\mathrm{d}[\mathrm{Fe_4S_4Cl_4}^{2-}]}{\mathrm{d}t} = \frac{\{1.7 \times 10^4 + 5.2 \times 10^7[\mathrm{H_2\overline{N(CH_2)_3CH_2}}^+]_0\}[\mathrm{PhS^-}]_0[\mathrm{Fe_4S_4Cl_4}^{2-}]}{1 + 2.8 \times 10^2[\mathrm{H_2\overline{N(CH_2)_3CH_2}}^+]_0} \quad (8)$$

Scheme 2. Since $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}]^+$ is such a weak acid, protonation of $[\mathrm{Fe_4S_4Cl_4}]^{2-}$ is slow at all concentrations of acid used. Consequently binding of $\mathrm{PhS^-}$ to the cluster is the more rapid process and is the first step under these conditions. Subsequent dissociation of the Fe–Cl bond can then occur to yield the product, in a pathway which is not associated with the acid at any stage. However, at high concentrations of acid, interaction of $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}]^+$ with the cluster occurs, after binding of $\mathrm{PhS^-}$, and this further labilises the cluster towards dissociation of the chloro-group. The simplicity of the kinetics are consistent with this "interaction" being either complete proton transfer from $[\mathrm{\overline{NH_2(CH_2)_3CH_2}}]^+$ to the cluster (as shown in Scheme 2), or merely a hydrogen bonding interaction. Based on the kinetic data, these two possibilities are indistinguishable. Using the steady state treatment[15] the rate law derived from this mechanism is that shown in eqn. (9).

$$\frac{-\mathrm{d}[\mathrm{Fe_4S_4Cl_4}^{2-}]}{\mathrm{d}t} = \frac{\{(k_1k_2 + k_1k_5[\mathrm{\overline{NH_2(CH_2)_3CH_2}}^+]_0)/(k_{-1} + k_2)\}[\mathrm{PhS^-}]_0[\mathrm{Fe_4S_4Cl_4}^{2-}]}{1 + \{k_5[\mathrm{\overline{NH_2(CH_2)_3CH_2}}^+]_0/(k_{-1} + k_2)\}} \quad (9)$$

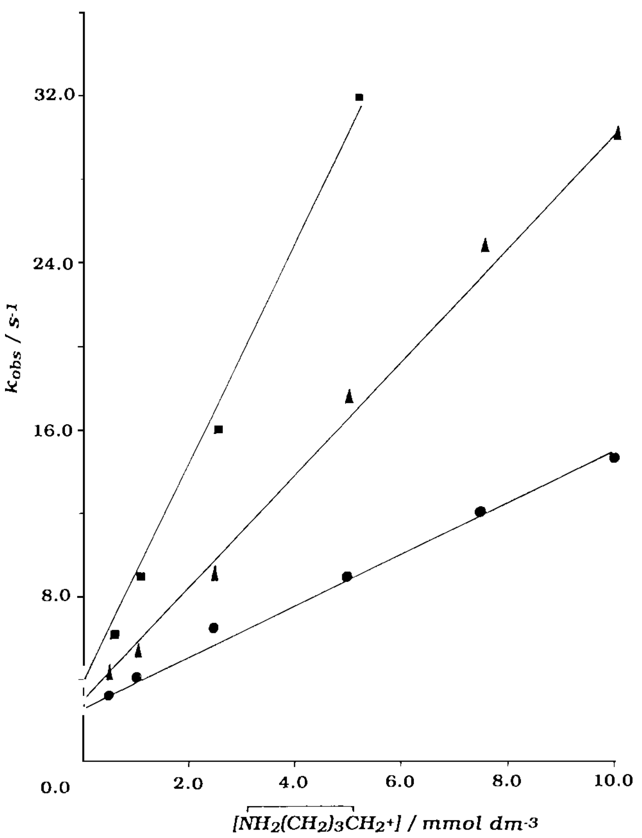
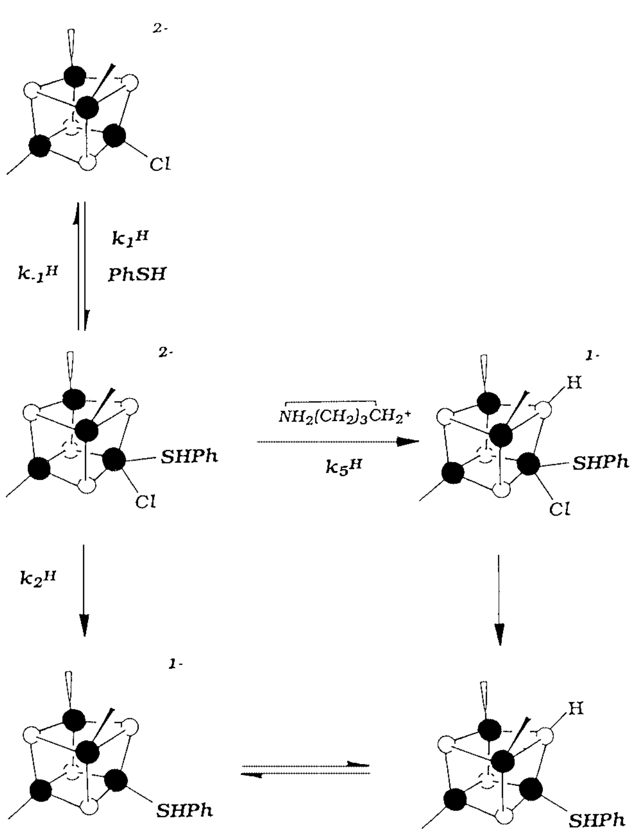


Fig. 2 Dependence of k_{obs} on the concentration of $[NH_2(CH_2)_3CH_2]^+$ for the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhSH in MeCN at 25.0 °C {ionic strength = 0.1 mol dm^{-3} ($[NBu^n_4][BF_4]$}; $[Fe_4S_4Cl_4^{2-}] = 0.05$ mmol dm^{-3}. Data points correspond to: $[NH_2(CH_2)_3CH_2^+] = 0–10$ mmol dm^{-3}, [PhSH] = 1.25 (■), 0.63 (▲) or 0.31 mmol dm^{-3} (●). Lines drawn are those defined by eqn. (10), and the parameters in the text.



Scheme 3 Mechanism for the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhSH in the presence of $[NH_2(CH_2)_3CH_2]^+$ in MeCN.

Comparison of eqns. (8) and (9) gives: $k_1k_2/(k_{-1} + k_2) = 1.7 \times 10^4$ dm^3 mol^{-1}; $k_1k_5/(k_{-1} + k_2) = 5.2 \times 10^7$ dm^6 mol^{-2} and $k_5/(k_{-1} + k_2) = 2.8 \times 10^2$ dm^3 mol^{-1}. Simple inspection of these then gives $k_1 = 1.9 \times 10^5$ dm^3 mol^{-1} s^{-1} and $k_{-1}/k_2 = 10.2$ and $k_5/k_2 = 3.1 \times 10^5$ dm^3 mol^{-1}. The earlier study on the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^- alone gave $k_2 = 2.5 \times 10^2$ s^{-1}, and hence we can determine $k_5 = 7.8 \times 10^5$ dm^3 mol^{-1} s^{-1} and $k_{-1} = 2.6 \times 10^3$ s^{-1}.

The correctness of this analysis is indicated by the values of the elementary rate constants that we have determined. Using these values we can calculate that $K_1 = k_1/k_{-1} = 73$ dm^3 mol^{-1}. This is in excellent agreement with $K_1 = 68.4$ dm^3 mol^{-1}, determined directly in the earlier study (eqn. (7))[8] of the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^- in the absence of acid.

Kinetics of the reaction with $[NH_2(CH_2)_3CH_2]^+$ and PhSH

Studies on the analogous reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhSH in the presence of $[NH_2(CH_2)_3CH_2]^+$ shows similar kinetic behaviour to that with PhS^-. The dependence of the rate on the concentrations of $[NH_2(CH_2)_3CH_2]^+$ and PhSH is illustrated in Fig. 2, and the mechanism is shown in Scheme 3. This mechanism is identical to that in Scheme 2, except PhSH replaces PhS^-, and consequently the derived rate law is analogous to eqn. (9), as shown in eqn. (10). Analysis of the data gives: $k_0 = 2.0$ s^{-1}; $k_1^Hk_2^H/(k_{-1}^H + k_2^H) = 1 \times 10^3$ dm^3 mol^{-1} s^{-1} and $k_1^Hk_5^H/(k_{-1}^H + k_2^H) = 4.2 \times 10^6$ dm^6 mol^{-2} s^{-1} and $k_5^H/(k_{-1}^H + k_2^H) \le 10$ dm^3 mol^{-1}. It is worth noting that the reaction with PhSH is sufficiently slow that the dissociative pathway (k_0) makes a significant contribution to the rate of the reaction. This dissociative pathway has been observed in earlier studies[8] and the value of k_0 measured here is in excellent agreement with that determined earlier. The rapidity of the reaction with PhS^- means that k_0 makes an insignificant contribution to the total rate.

Comparison of the values obtained with PhSH with those involving PhS^- (eqn. (9)) shows that both the acid-independent and acid-dependent pathways are 15 ± 2 times faster in the PhS^- system. This is consistent with PhS^- being a better nucleophile than PhSH towards $[Fe_4S_4Cl_4]^{2-}$.

Effect of $NH(CH_2)_3CH_2$ on the kinetics with PhS^- in presence of $[NH_2(CH_2)_3CH_2]^+$

The effect that $NH(CH_2)_3CH_2$ has on the rate of the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^- in the presence of $[NH_2(CH_2)_3CH_2]^+$ is shown in Fig. 3. It is evident that in the presence of $NH(CH_2)_3CH_2$ the rate increases, and the reaction is extremely sensitive to even small amounts of this base.

The kinetics in the presence of $NH(CH_2)_3CH_2$ is described by eqn. (11). The first (PhS^--dependent) term in eqn. (11) is identical to eqn. (8) and describes the data in Fig. 1. The most important feature to note is that the kinetics of this pathway is

$$\frac{-d[Fe_4S_4Cl_4^{2-}]}{dt} = \frac{(k_0 + \{k_1^Hk_2^H/(k_{-1}^H + k_2^H) + k_1^Hk_5^H/(k_{-1}^H + k_2^H)[NH_2(CH_2)_3CH_2^+]_0\}[PhSH]_0)[Fe_4S_4Cl_4^{2-}]}{1 + \{k_5^H[NH_2(CH_2)_3CH_2^+]_0/(k_{-1}^H + k_2^H)\}} \quad (10)$$

$$\frac{-d[Fe_4S_4Cl_4^{2-}]}{dt} = \frac{\{1.7 \times 10^4 + 5.2 \times 10^7[NH_2(CH_2)_3CH_2^+]_0\}[PhS^-]_0}{1 + 2.8 \times 10^2[NH_2(CH_2)_3CH_2^+]_0} + \{7.0 \times 10^4 + 2.5 \times 10^7[NH_2(CH_2)_3CH_2^+]_0\}[NH(CH_2)_3CH_2]_0[Fe_4S_4Cl_4^{2-}] \quad (11)$$

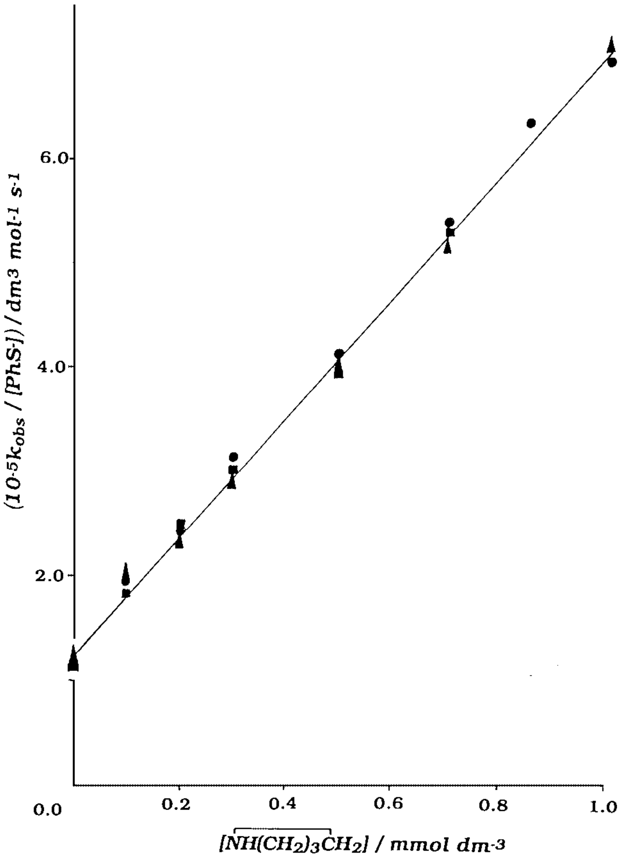
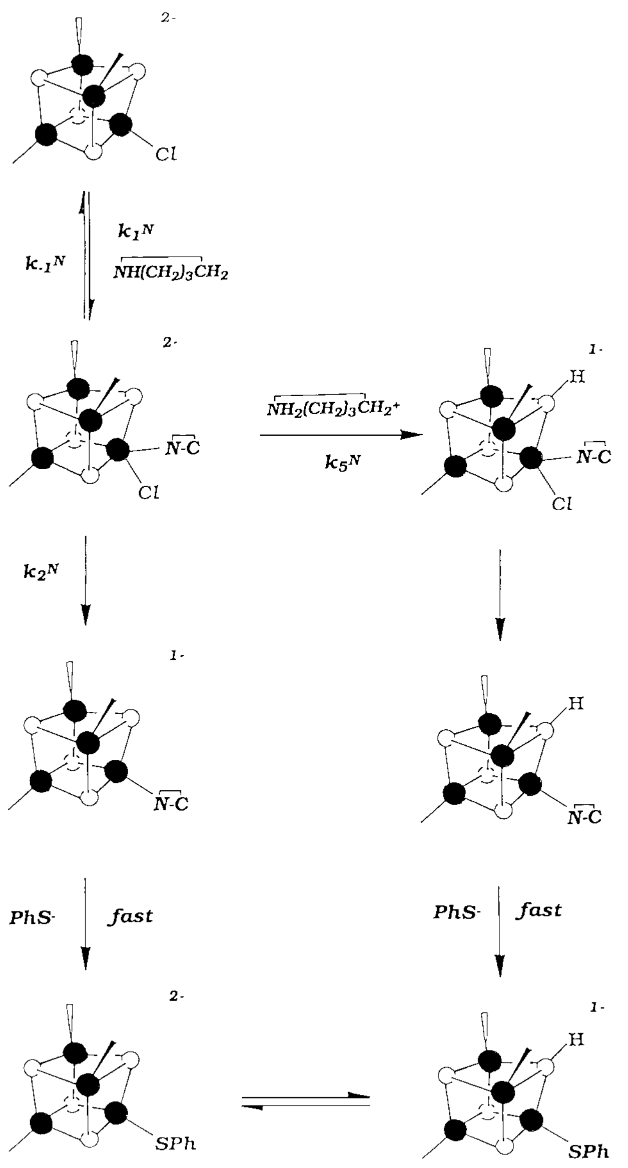


Fig. 3 Dependence of $k_{obs}/[PhS^-]$ on the concentration of $\overline{NH(CH_2)_3CH_2}$ for the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^- in the presence of $[\overline{NH_2(CH_2)_3CH_2}]^+$ (5.0 mmol dm^{-3}) in MeCN at 25.0 °C {ionic strength = 0.1 mol dm^{-3} ($[NBu^n_4][BF_4]$}; $[Fe_4S_4Cl_4^{2-}] = 0.05$ mmol dm^{-3}. Data points correspond to: $[PhS^-] = 1.25$ (■), 0.63 (▲) or 0.31 mmol dm^{-3} (●). Line drawn is that defined by eqn. (11).

unaffected by the addition of $\overline{NH(CH_2)_3CH_2}$. This validates our analysis of the data in Fig. 1. The second ($\overline{NH(CH_2)_3CH_2}$-dependent) term in eqn. (11) is only evident when $\overline{NH(CH_2)_3CH_2}$ has been added to the solution. Note that if the concentrations of $[\overline{NH_2(CH_2)_3CH_2}]^+$ and PhS^- are constant, the value of k_{obs} varies linearly with $[\overline{NH(CH_2)_3CH_2}]_0$.

The similarity of the PhS^-- and $\overline{NH(CH_2)_3CH_2}$-dependent terms is self-evident; the two are identical with $[\overline{NH(CH_2)_3CH_2}]_0$ replacing $[PhS^-]_0$. This suggests the mechanism in Scheme 4.



Scheme 4 Pathway for the substitution reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^- in the presence of $[\overline{NH_2(CH_2)_3CH_2}]^+$ and $\overline{NH(CH_2)_3CH_2}$ in MeCN. This pathway operates in competition to the pathway shown in Scheme 2.

Since $[\overline{NH_2(CH_2)_3CH_2}]^+$ is a weak acid, $\overline{NH(CH_2)_3CH_2}$ is a relatively strong base and is consequently able to compete with PhS^- in binding to the cluster. Application of the steady state treatment[15] to this mechanism gives the rate law (12), and comparison of eqns. (11) and (12) gives $k_1^N k_2^N/(k_{-1}^N + k_2^N) = 7.0 \times 10^4$ dm^3 mol^{-1} s^{-1}, $k_1^N k_5^N/(k_{-1}^N + k_2^N) = 2.5 \times 10^7$ dm^6 mol^{-2} s^{-1} and $k_5^N/(k_{-1}^N + k_2^N) \le 20$ dm^3 mol^{-1}.

The pK_a of $[\overline{NH_2(CH_2)_3CH_2}]^+$ in MeCN

In the discussion so far we have gone to some lengths to demonstrate two key points concerning mixtures of PhS^- and $[\overline{NH_2(CH_2)_3CH_2}]^+$ in MeCN: (i) the concentration of PhS^- is that added to the solution and (ii) the concentration of $\overline{NH(CH_2)_3CH_2}$ must be less than 0.1 mmol dm^{-3}, even at the highest concentration of acid used. Both these features are in marked contrast to the behaviour of mixtures of PhS^- and $[NHEt_3]^+$ {eqns. (3)–(6)}, and indicate that the simple protolytic equilibrium (13) lies to the left hand side. We have laboured this

$$[\overline{NH_2(CH_2)_3CH_2}]^+ + PhS^- \rightleftharpoons \overline{NH(CH_2)_3CH_2} + PhSH \quad (13)$$

point because these experimental observations are inconsistent with the literature value[6] of pK_a = 19.6 for $[\overline{NH_2(CH_2)_3CH_2}]^+$, as we will now discuss.

Our earlier studies[5] on the reactions of Fe–S-based clusters

$$\frac{-d[Fe_4S_4Cl_4^{2-}]}{dt} = \frac{\{(k_1k_2 + k_1k_5[\overline{NH_2(CH_2)_3CH_2}^+]_0)/(k_{-1} + k_2)\}[PhS^-]_0}{1 + \{k_5[\overline{NH_2(CH_2)_3CH_2}^+]_0/(k_{-1} + k_2)\}} +$$

$$\frac{\{(k_1^N k_2^N + k_1^N k_5^N[\overline{NH_2(CH_2)_3CH_2}^+]_0)/(k_{-1}^N + k_2^N)\}[\overline{NH(CH_2)_3CH_2}]_0)[Fe_4S_4Cl_4^{2-}]}{1 + \{k_5^N[\overline{NH_2(CH_2)_3CH_2}^+]_0/(k_{-1} + k_2^N)\}} \quad (12)$$

in the presence of $[\mathrm{NHEt_3}]^+$ showed that at least 85% of the PhS^- is converted into PhSH when there is a twofold excess of $[\mathrm{NHEt_3}]^+$, which means for eqn. (3), $K_A \geq 4$, from which we can estimate that for PhSH, $\mathrm{p}K_a \geq 19.3$ in MeCN.

Using the literature $\mathrm{p}K_a$ and $K_H = 31.6$ for $[\mathrm{NH_2(CH_2)_3CH_2}]^+$, the protolytic equilibrium constant between $[\mathrm{NH_2(CH_2)_3CH_2}]^+$ and PhS^- shown in eqn. (14) can be calculated, $K_B \geq 7.9$ (K_H is the homoconjugation constant for the equilibrium $[\mathrm{NH_2(CH_2)_3CH_2}]^+ + \mathrm{NH(CH_2)_3CH_2} \rightleftharpoons [\mathrm{NH(CH_2)_3CH_2}]_2\text{-}\mathrm{H}^+$). The value of K_B thus obtained is inconsistent with our experimental findings, as can be illustrated in two ways.

$$2[\mathrm{NH_2(CH_2)_3CH_2}]^+ + \mathrm{PhS}^- \overset{K_B}{\rightleftharpoons} [\mathrm{NH(CH_2)_3CH_2}]_2\mathrm{H}^+ + \mathrm{PhSH} \quad (14)$$

First, when $[\mathrm{NH_2(CH_2)_3CH_2}^+]_0 = 10.0$ mmol dm^{-3} and $[\mathrm{PhS}^-] = 0.5$ mmol dm^{-3} the experiments with $\mathrm{NH(CH_2)_3CH_2}$ show that in solution $[\mathrm{NH(CH_2)_3CH_2}]_e \leq 0.1$ mmol dm^{-3}. Hence, we can calculate $K_B \leq 8 \times 10^{-2}$, at least one hundred times smaller than the value calculated using the literature data!

Secondly, using $K_B = 7.9$, we can calculate that mixing $[\mathrm{NH_2(CH_2)_3CH_2}^+] = 10.0$ mmol dm^{-3} and $[\mathrm{PhS}^-]_0 = 0.5$ mmol dm^{-3} results at equilibrium in the following species being present: $[\mathrm{PhSH}]_e = 0.46$, $[\{\mathrm{NH(CH_2)_3CH_2}\}_2\mathrm{H}^+]_e = 0.10$- $[\mathrm{NH(CH_2)_3CH_2}]_e = 0.32$, $[\mathrm{PhS}^-]_e = 0.04$ and $[\mathrm{NH_2(CH_2)_3CH_2}^+]_e = 9.48$ mmol dm^{-3}. If all these species are present, all the pathways we have described so far in this paper (PhS^- in the presence of $[\mathrm{NH_2(CH_2)_3CH_2}]^+$; PhSH in the presence of $[\mathrm{NH_2(CH_2)_3CH_2}]^+$; and the effect of $\mathrm{NH(CH_2)_3CH_2}$) would contribute to the total rate of the reaction. Using these calculated concentrations we can calculate the contributions to the total rate made, under these conditions, by: (i) PhSH-dependent pathway (eqn. (9)), $k_{obs} = 21$ s^{-1} and (ii) the $\mathrm{NH(CH_2)_3CH_2}$-dependent pathway (second term of eqn. (10), $k_{obs} = 99$ s^{-1}. Yet under these conditions we find experimentally $k_{obs} = 68$ s^{-1}!.

The conclusion from these two examples must be that the literature value for the $\mathrm{p}K_a$ of $[\mathrm{NH_2(CH_2)_3CH_2}]^+$ cannot be applicable in our case. The reason for this is not entirely clear. The literature $\mathrm{p}K_a$ was determined by a potentiometric method[16] with very low (*ca.* 1.0 mmol dm^{-3}) water present in the MeCN. Although we use MeCN freshly distilled from $\mathrm{CaH_2}$ and glassware from the oven, we suspect that the water content of our MeCN is significantly higher than 1.0 mmol dm^{-3}. It has been pointed out before[17] that MeCN is a relatively inert solvent and even traces (μmol dm^{-3}) of ammonia or water can interfere with studies involving ionisation of very weak acids (such as $[\mathrm{NH_2(CH_2)_3CH_2}]^+$). The literature data are reported at an ionic strength of less than 0.01 mol dm^{-3}, and have been corrected by use of one of the Debye–Hückel equations. In contrast, all our experiments were performed at a constant ionic strength of 0.1 mol dm^{-3}. However, the effect of ionic strength would not be expected to account for the large difference in $\mathrm{p}K_a$ that we propose. It is important to emphasise that our kinetic results are entirely reproducible and so any trace impurities in the solvent are present in reproducibly constant amounts.

The $\mathrm{p}K_a$ of $[\mathrm{NH_2(CH_2)_3CH_2}]^+$ which is consistent with our observations can be calculated since, as shown above, $K_B \leq 8 \times 10^{-2}$, and hence $\mathrm{p}K_a = 21.6$ for $[\mathrm{NH_2(CH_2)_3CH_2}]^+$ (assuming $K_H = 31.6$ is correct). Evidence that our $\mathrm{p}K_a$ is correct comes from a kinetic study on $[\mathrm{Fe_4S_4(SEt)_4}]^{2-}$.

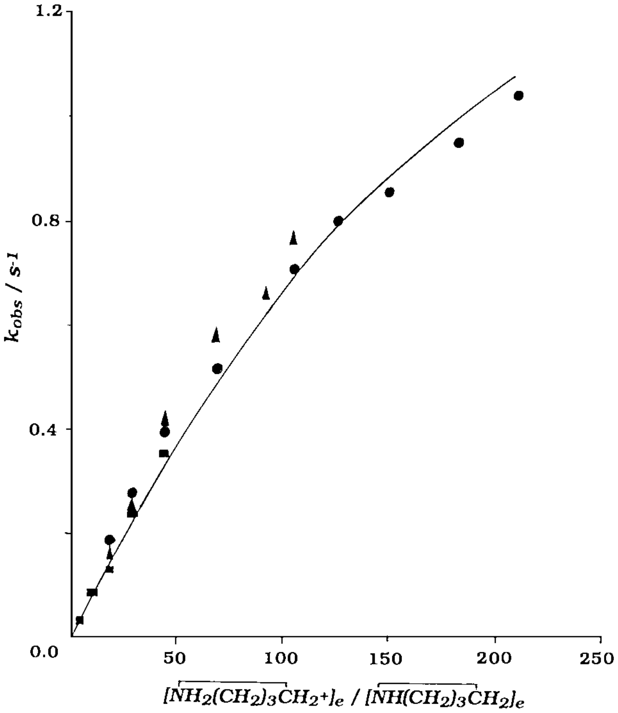


Fig. 4 Dependence of k_{obs} on $[\mathrm{NH_2(CH_2)_3CH_2}^+]_e/[\mathrm{NH(CH_2)_3CH_2}]_e$ for the reaction between $[\mathrm{Fe_4S_4(SEt)_4}]^{2-}$ and PhS^- in the presence of $[\mathrm{NH_2(CH_2)_3CH_2}]^+$ in MeCN at 25.0 °C {ionic strength = 0.1 mol dm^{-3} ($[\mathrm{NBu^n_4}][\mathrm{BF_4}]$}; $[\mathrm{Fe_4S_4(SEt)_4}^{2-}] = 0.05$ mmol dm^{-3}. Data points correspond to: $[\mathrm{NH_2(CH_2)_3CH_2}^+] = 1.0$–$20.0$ mmol dm^{-3}; $[\mathrm{PhS}^-] = 0.5$ (●), 1.0 (▲) or 1.0 mmol dm^{-3}, $[\mathrm{NH(CH_2)_3CH_2}] = 0.2$ mmol dm^{-3} (■). Curve drawn is that defined by eqn. (16) and the parameters in the text.

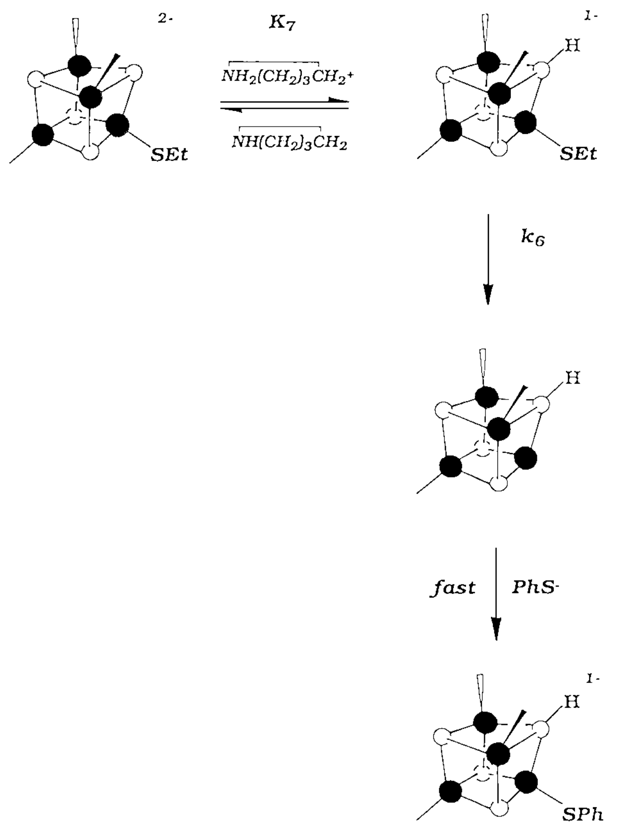
Reaction between $[\mathrm{Fe_4S_4(SEt)_4}]^{2-}$ and PhS^- in the presence of $[\mathrm{NH_2(CH_2)_3CH_2}]^+$

The kinetics of the reaction shown in equation (15) has been

$$[\mathrm{Fe_4S_4(SEt)_4}]^{2-} + \mathrm{PhS}^- \xrightarrow{[\mathrm{NH_2(CH_2)_3CH_2}]^+} [\mathrm{Fe_4S_4(SEt)_3(SPh)}]^{2-} + \mathrm{EtS}^- \quad (15)$$

studied. The rate of the reaction shows a dependence on $[\mathrm{NH_2(CH_2)_3CH_2}^+]_e/[\mathrm{NH(CH_2)_3CH_2}]_e$ as shown in Fig. 4. The concentrations of $[\mathrm{NH_2(CH_2)_3CH_2}^+]_e$ and $[\mathrm{NH(CH_2)_3CH_2}]_e$ were calculated using eqn. (14) and our value $\mathrm{p}K_a = 21.6$ and $K_H = 31.6$ for $[\mathrm{NH_2(CH_2)_3CH_2}]^+$ together with $\mathrm{p}K_a = 19.3$ for PhSH. Confirmation of this behaviour was obtained from studies in which was $\mathrm{NH(CH_2)_3CH_2}$ also added to the solution (see Fig. 4). Clearly, the rate of the reaction exhibits a non-linear dependence on $[\mathrm{NH_2(CH_2)_3CH_2}^+]_e/[\mathrm{NH(CH_2)_3CH_2}]_e$. This is analogous to the behaviour observed in the presence of $[\mathrm{NHEt_3}]^+$, and is consistent with the previously established mechanism[18] shown in Scheme 5, with the associated rate law (16). This rate law describes an acid-catalysed substitution mechanism in which protonation of the cluster rapidly precedes rate-limiting dissociation of the thiolate. Subsequent rapid binding of the nucleophile completes the substitution. Analysis of these data gives $k_6 = 2.5$ s^{-1}, identical to the value obtained in the study with $[\mathrm{NHEt_3}]^+$, and $K_7 = 3.6 \times 10^{-3}$. Since $K_7 = K_a^{(\mathrm{NH_2(CH_2)_3CH_2})}K_H/K_a^{(\mathrm{Fe_4S_4(SEt)_4})}$ we can calculate $\mathrm{p}K_a^{(\mathrm{Fe_4S_4(SEt)_4})} = 17.8$, in excellent agreement with the value

$$\frac{-\mathrm{d}[\mathrm{Fe_4S_4(SEt)_4}^{2-}]}{\mathrm{d}t} = \frac{(k_6K_7[\mathrm{NH_2(CH_2)_3CH_2}^+]_e/[\mathrm{NH(CH_2)_3CH_2}]_e)[\mathrm{Fe_4S_4(SEt)_4}^{2-}]}{1 + (K_7[\mathrm{NH_2(CH_2)_3CH_2}^+]_e/[\mathrm{NH(CH_2)_3CH_2}]_e)} \quad (16)$$



Scheme 5 Mechanism for the reaction between $[Fe_4S_4(SEt)_4]^{2-}$ and PhS^- in the presence of $[NH_2(CH_2)_3CH_2]^+$ in MeCN. For simplicity only one ethanethiolate ligand shown.

obtained from the studies with $[NHEt_3]^+$ (18.0).[19] In contrast, calculating the concentrations of $[NH_2(CH_2)_3CH_2{}^+]_e$ and $[NH(CH_2)_3CH_2]_e$, and analysing the data using $pK_a = 19.6$ for $[NH_2(CH_2)_3CH_2]^+$, we obtain $k_6 = 2.5\ s^{-1}$ and $K_7 = 8.35 \times 10^{-3}$ which results in $pK_a^{(Fe_4S_4(SEt)_4)} = 16.0$, two units lower than the value obtained in the earlier studies using $[NHEt_3]^+$!

To establish that $pK_a = 21.6$ for $[NH_2(CH_2)_3CH_2]^+$ is *uniquely* the best fit to these data we have explored the effect of varying the pK_a on the internal consistency of our analysis. For each pK_a (pK_a^{used}), $[PhSH]_e$, $[NH_2(CH_2)_3CH_2{}^+]_e$ and $[NH(CH_2)_3CH_2]_e$ were calculated and a graph analogous to Fig. 4 was plotted. Analysis of it gave the corresponding value of K_7, and using this value, together with $pK_a = 17.8$ for the cluster, the pK_a of $[NH_2(CH_2)_3CH_2]^+$ was calculated (pK_a^{calc}). The results are illustrated in Fig. 5 and show that only when $pK_a \approx 21.5$ does this lead to an internally consistent analysis.

That the reaction of $[Fe_4S_4(SEt)_4]^{2-}$ with PhS^- is acid catalysed by $[NH_2(CH_2)_3CH_2]^+$ must be because $k_7 \times [NH_2(CH_2)_3CH_2{}^+]_e \geq k_6$ (*i.e.* $k_7 \geq 1.3 \times 10^3\ dm^3\ mol^{-1}\ s^{-1}$). As we will see in a later section, this limit of the rate constant for protonation of the cluster core is consistent with that estimated for $[Fe_4S_4Cl_4]^{2-}$.

Other systems

Before leaving this discussion about the pK_a of $[NH_2(CH_2)_3CH_2]^+$ there are data in the literature which indicate that $pK_a = 19.6$ is inappropriate. The rate constants for proton transfer from $[Ru(\eta^5\text{-}C_5H_5)H(PPh_3)_2]^+$ to $NH(CH_2)_3CH_2$ and $NH(CH_2)_4CH_2$ (pK_a of conjugate acid = 18.9) have been measured.[20] It has been pointed out that the rate of proton transfer with $NH(CH_2)_3CH_2$ is faster because of the pK_a values of the conjugate acids. However, the reaction with $NH(CH_2)_3CH_2$ is nearly 200 times faster than with $NH(CH_2)_4CH_2$, yet the difference in the literature pK_a values of the two conjugate acids is only 0.7. Considering how similar these two bases are structurally, this would be a proton transfer reaction which is remarkably sensitive to small changes in the base strength. In fact it would correspond to a Brönsted $\beta \gg 1$; this value is usually positive and less than unity.[21] However, consider the results in the light of our estimate of the pK_a for $[NH_2(CH_2)_3CH_2]^+$. Now the behaviour is much more reasonable since the differences in pK_a is 2.7, corresponding to a Brönsted $\beta < 1$.

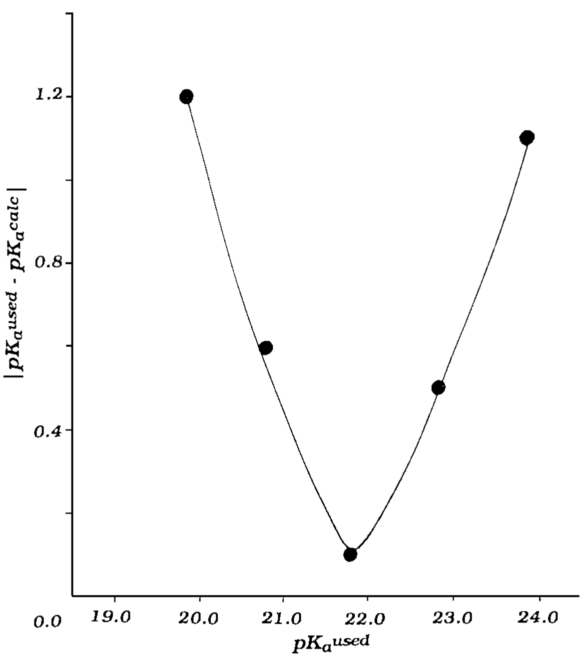


Fig. 5 Graph of $|pK_a^{used} - pK_a^{calc}|$ *versus* pK_a^{used} (where pK_a is that of $[NH_2(CH_2)_3CH_2]^+$) showing how only when $pK_a^{used} \approx 21.5$ the kinetic data for the reaction between $[Fe_4S_4(SEt)_4]^{2-}$ and PhS^- in the presence of $[NH_2(CH_2)_3CH_2]^+$ in MeCN at 25.0 °C give an internally consistent result. See text for meaning of the superscripts "used" and "calc".

The maximum rate of protonation of the cluster core

Prior to the work described in this paper, the substitution reactions of all Fe–S-based clusters exhibited acid-catalysed mechanisms in which the reaction was rate-limited by the act of substitution after a rapid protonation step. Consequently it has only been possible to estimate a lower limit to the rate constant for protonation of the cluster core. Thus, even at the lowest concentration of $[NHEt_3]^+$ used with $[Fe_4S_4Cl_4]^{2-}$ ($[NHEt_3{}^+]_e = 1.25\ mmol\ dm^{-3}$) protonation must be complete within the dead-time of the stopped-flow apparatus (2 ms) and hence $k_3 \geq 2 \times 10^5\ dm^3\ mol^{-1}\ s^{-1}$.

In the study of the reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhS^- in the presence of $[NH_2(CH_2)_3CH_2]^+$ we have shown that PhS^- binds initially to the cluster with $k_1 = 1.9 \times 10^5\ dm^3\ mol^{-1}\ s^{-1}$. Thus, at the lowest concentration of PhS^- used in this study ($0.25\ mmol\ dm^{-3}$), the rate of protonation of $[Fe_4S_4Cl_4]^{2-}$ by $[NH_2(CH_2)_3CH_2]^+$ must be at least ten times slower than the rate of PhS^- binding, even at the highest concentration of acid used ($10\ mmol\ dm^{-3}$). This allows us to calculate an upper limit for the protonation rate constant, $k_3 \leq 4.8 \times 10^2\ dm^3\ mol^{-1}\ s^{-1}$. This rate constant is that for a protonation which is thermodynamically unfavourable by $\Delta pK_a = 18.8\text{–}21.6 = -2.8$, and some relatively simple considerations allow us to estimate k_3 for a thermodynamically favourable reaction with $\Delta pK_a = +1.0$.

The general relationship between the rate constant of protonation (k_3) and the equilibrium constant (K_3) for reaction (17) is given by the Brönsted equation[21] (18), where G_A and a

$$[Fe_4S_4Cl_4]^{2-} + [NHR_3]^+ \overset{K_3}{\rightleftharpoons} [Fe_4S_3(SH)Cl_4]^- + NR_3 \quad (17)$$

$$k_3 = G_A K_3^{a} \quad (18)$$

are constants for a series of similar acids, with the Brönsted coefficient $a \le 1$. Eqn. (18) holds for a thermodynamically unfavourable proton-transfer reaction (*i.e.* $pK_a^{Fe_4S_4Cl_4} - pK_a^{NHR_3}$ is negative). When $pK_a^{Fe_4S_4Cl_4} - pK_a^{NHR_3}$ is zero the behaviour starts to change such that when $pK_a^{Fe_4S_4Cl_4} - pK_a^{NHR_3}$ is positive k_3 is independent of the thermodynamic driving force of the reaction. In general, for bases containing formal lone pairs of electrons, k_3 levels off at the diffusion-controlled rate ($k_{diff} \approx 1 \times 10^{10}$ dm^3 mol^{-1} s^{-1}). When there is considerable structural and/or electronic rearrangement to one of the partners upon proton transfer k_3 will be less than k_{diff} even for a thermodynamically favourable reaction.

Using eqn. (18) and our estimate of $k_3 \le 4.8 \times 10^2$ dm^3 mol^{-1} s^{-1} for protonation of $[Fe_4S_4Cl_4]^{2-}$ when $\Delta pK_a = -2.8$, we can estimate that, when $\Delta pK_a = +1.0$, $k_3 \le 4.8 \times 10^6$ dm^3 mol^{-1} s^{-1} (assuming $a \le 1$), and combining this with the lower limit established above the limits to the rate constant for protonation of the Fe_4S_4 core are $2 \times 10^5 \le k_3 \le 4.8 \times 10^6$ dm^3 mol^{-1} s^{-1}.

That this value is 10^4–10^5 times smaller than the diffusion-controlled limit means that there is an intrinsic barrier to protonation of this cluster core.[22,23] The most likely origin of this barrier is structural, in particular bond length reorganisations that have to occur upon protonation. Within the cluster framework, protonation of a single μ_3-S cannot occur in isolation; the whole of the cluster core has to respond. The three Fe–S bonds connected to the protonated sulfur will be the most affected leading to a distortion along the threefold axis, but this will have repercussions on all the other, inter-connected bonds. By analogy it is worth noting that a tetragonal distortion of the cube has been structurally well defined upon single electron reduction of $\{Fe_4S_4\}^{2+}$ clusters.[24]

There is evidence that, in general, protonation at μ-O and μ-S sites is slow.[22,23,25] This has been attributed to both electronic and geometric rearrangements upon protonation (*i.e.* the significant π bonding with the d orbitals of the metals and the change in M–O bond distances).

Slow proton transfer has been observed at Fe–S clusters inside proteins, in particular to the $\{Fe_3S_4\}$ cluster of a mutant of ferredoxin I from *Azotobacter vinelandii*.[26] In the wild type protein it is proposed that an aspartate (Asp-15) mediates the proton transfer from the solvent to the cluster site. Construction of the D15N mutant (in which the aspartate is replaced by an asparagine) results in protonation becoming slow with a directly measured rate constant, $k = 3 \times 10^7$ dm^3 mol^{-1} s^{-1}. The authors pointed out that this is 10^3–10^4 times slower than a diffusion-controlled process. Clearly, inside a protein matrix the Fe–S-based clusters geometries may be optimised to facilitate the proton transfer, but it is only in this paper that we have shown that protonation of Fe–S clusters can inherently be slower than the diffusion-controlled limit.

Acknowledgements

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