DALTON COMMUNICATION

Single protonation labilises but double protonation inhibits substitution of $[Fe_4S_4Cl_4]^{2-}$

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Successive protonation of $[Fe_4S_4(SPh)_4]^{2-}$ progressively labilises the cluster towards substitution of the thiolate ligands, whereas single protonation of $[Fe_4S_4Cl_4]^{2-}$ catalyses, but diprotonation inhibits, substitution of the chloro-ligands.

The acid catalysis of substitution reactions is a recurring theme in organic, inorganic and biological chemistry. In this paper we report an unusual effect of protonation on substitution reactions: *single protonation of* $[Fe_4S_4Cl_4]^{2-}$ *catalyses the rate of substitution of the chloro-ligands, but diprotonation inhibits substitution.*

The acid-catalysed substitution reaction [typified by equation (1)] is entirely general for both synthetic and extracted biological iron–sulfur-based clusters.[1,2] Earlier studies[2,3] in MeCN, with the relatively weak acid $[NHEt_3]^+$ ($pK_a = 18.46$)[3] showed the following general mechanistic features. (i) Protonation of a thiolate ligand is not labilising.[1] (ii) Labilisation is a consequence of protonation of the cluster core, probably at a μ_3-S site.[4] (iii) The mechanism is dissociative when X = RS,[5] but associative when X = halide.[1] (iv) Protonation catalyses substitution irrespective of whether X = RS or halide.[1]

$$[Fe_4S_4X_4]^{2-} \xrightarrow[[NHR_3]^+]{RSH} [Fe_4S_4X_3(SHR)]^- + X^- \qquad (1)$$

With the stronger acid $[lutH]^+$ (lut = 2,6-dimethylpyridine; $pK_a = 14.1$[3]) we observe (not unexpectedly) that diprotonation of $[Fe_4S_4X_4]^{2-}$ (X = PhS or Cl) occurs, but the effect on the substitution labilities of the two clusters is dramatically different.

The kinetics of the substitution reaction between $[Fe_4S_4(SPh)_4]^{2-}$ and EtSH, in the presence of an excess of $[lutH]^+$, follow the same pattern as with $[NHEt_3]^+$, except that the reaction is faster (Fig. 1). Thus, the rate of reaction exhibits a first-order dependence on the concentration of cluster and a non-linear dependence on $[lutH^+]/[lut]$. In the reactions reported in this paper the free thiol acts only as the nucleophile. The thiol is a much weaker acid than $[NHEt_3]^+$ or $[lutH]^+$ in MeCN and does not significantly contribute to the protonation of the cluster. Thus in the reaction of $[Fe_4S_4(SPh)_4]^{2-}$, varying the concentration of EtSH ([EtSH] = 1–10 mmol dm^{-3}), whilst maintaining $[lutH^+]/[lut] = 4.0$, does not affect the rate of the reaction ($k_{obs} = 0.25 \pm 0.01\ s^{-1}$). Similar behaviour was observed in the earlier studies[5] with $[NHEt_3]^+$.

The data in Fig. 1 are consistent with the dissociative pathways shown in Scheme 1 and described by the general rate law of equation (2). From the earlier studies[1] with $[NHEt_3]^+$ it is known that protonation of the first μ_3-S is associated with $pK_a = 18.6$ for the cluster. Hence, in the studies with $[lutH^+]$, we can calculate $K_1^S = 3.2 \times 10^4$. Consequently, under the conditions reported herein, $K_1^S[lutH^+]/[lut] \gg 1$ and equation (2) simplifies to equation (3), with $k_3^S = 0.085 \pm 0.003\ s^{-1}$,

$$\frac{-d[Fe_4S_4]}{dt} = \frac{\{K_1^S k_3^S[lutH^+]/[lut] + K_1^S K_2^S k_4^S[lutH^+]^2/[lut]^2\}[Fe_4S_4]}{1 + K_1^S[lutH^+]/[lut] + K_1^S K_2^S[lutH^+]^2/[lut]^2} \qquad (2)$$

$$\frac{-d[Fe_4S_4]}{dt} = \frac{\{k_3^S + K_2^S k_4^S[lutH^+]/[lut]\}[Fe_4S_4]}{1 + K_2^S[lutH^+]/[lut]} \qquad (3)$$

$k_4^S = 0.39 \pm 0.02\ s^{-1}$ and $K_2^S = 0.38 \pm 0.02$; $pK_a^S = 13.7$. The sequence of protonation and substitution steps for the acid-catalysed substitution reaction of $[Fe_4S_4(SPh)_4]^{2-}$ is as follows. At all concentrations of $[lutH]^+$, it seems likely that a thiolate ligand is protonated but, as we have pointed out before,[1] protonation at this site is not labilising. At low values of $[lutH^+]/[lut]$, additional protonation of a single μ_3-S occurs and this labilises the thiol to dissociation. Consistent with this interpretation, we find that under these conditions, the rate of substitution is the same as that observed in earlier studies[5] using $[NHEt_3]^+$ ($k_3^S = 0.080 \pm 0.001\ s^{-1}$; Fig. 1 insert). At high values of $[lutH^+]/[lut]$ further protonation occurs and (by analogy with the earlier studies) this probably occurs at another μ_3-S atom. This further labilises the co-ordinated thiol. Subsequent rapid attack by EtSH completes the substitution.

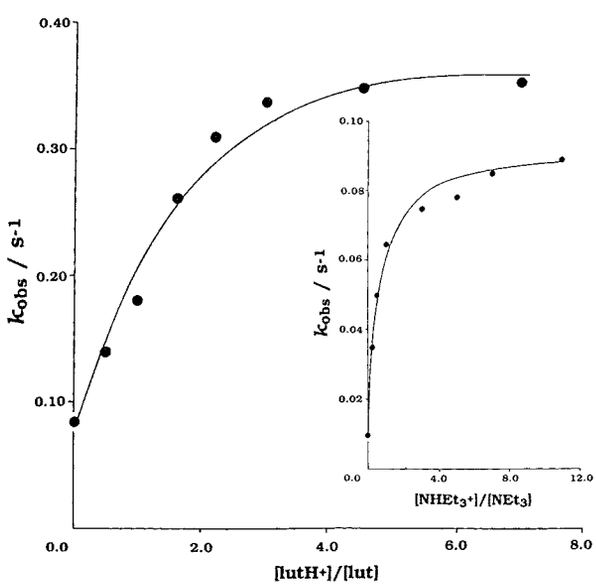
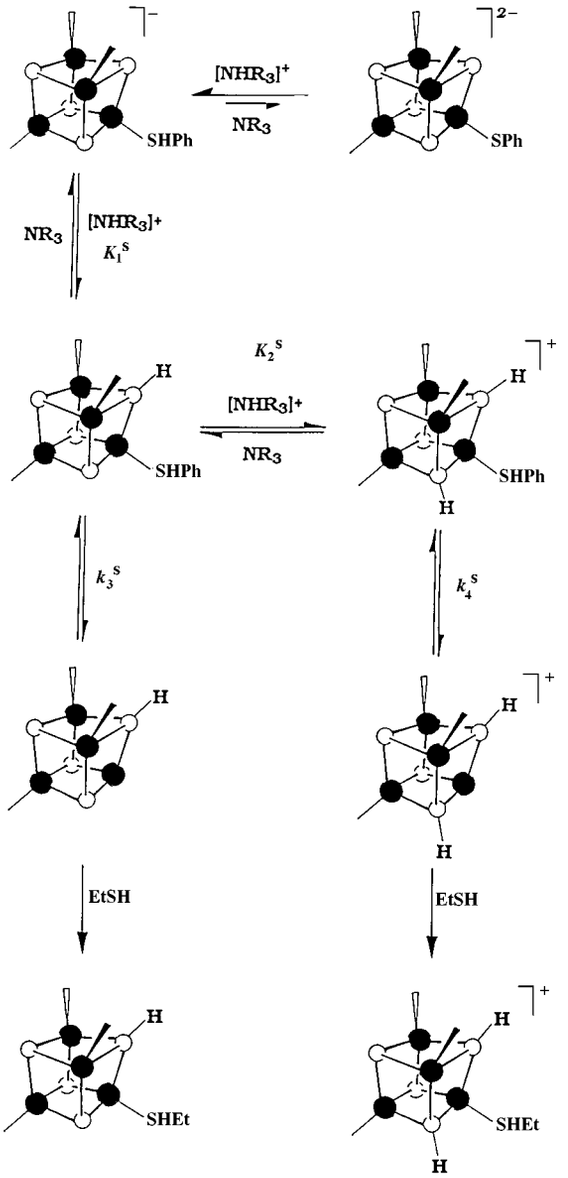


Fig. 1 The kinetics of the first substitution reaction of $[Fe_4S_4(SPh)_4]^{2-}$ with EtSH, in the presence of acid in MeCN at 25.0 °C. INSERT. Effect of single protonation: dependence of k_{obs} on $[NHEt_3^+]/[NEt_3]$. Curve and data from ref. 5. MAIN. Effect of diprotonation: dependence of k_{obs} on $[lutH^+]/[lut]$. Curve drawn is that defined by equation (3) and the values in the text. In MeCN, the protolytic equilibrium between $[lutH]^+$ and RS^- lies to the right hand side of $[lutH]^+ + RS^- \rightleftharpoons lut + RSH$. With an excess of $[lutH]^+$ the concentrations can be calculated as follows: $[lutH^+] = [lutH^+] - [RS^-]$ and $[lut] = [RSH] = [RS^-]$. The thiolate is supplied as the $[NEt_4]^+$ salt, and the acid as the $[BPh_4]^-$ salt



Scheme 1 Mechanism for the dissociative acid-catalysed substitution reactions of $[Fe_4S_4(SPh)_4]^{2-}$ (Fe = ●; S = ○). For clarity, only the PhS group undergoing substitution is shown

The substitution mechanisms of $[Fe_4S_4(SPh)_4]^{2-}$ are dissociative and thus the effect protonation has on the rate primarily reflects changes to the Fe–SPh bond strength. Initial protonation of the thiolate ligand weakens this Fe–S σ-bond but strengthens Fe-to-S π-back bonding. Consequently, this protonation has little effect on the rate of cluster substitution.[6] Additional protonation of one μ_3-S makes this atom a good π-electron acceptor which competes with the thiol for the electron density on Fe, thus labilising the thiol to dissociation. Further protonation, at another μ_3-S, additionally competes for the π-electron density of Fe and consequently further weakens, and labilises, the Fe–SHPh bond.

The kinetics of the substitution reaction between $[Fe_4S_4Cl_4]^{2-}$ and PhSH in the presence of an excess of $[lutH]^+$ shows two distinct differences from those of $[Fe_4S_4(SPh)_4]^{2-}$. (1) The reaction exhibits a first-order dependence on the concentration of PhSH. Thus, when $3.0 < [lutH^+]/[lut] < 11.0$, k_{obs} varies linearly as the concentration of PhSH is changed ($k_{obs}/[PhSH] = 4.0 \pm 0.5 \times 10^2$ dm^3 mol^{-1} s^{-1}). (2) The rate of the reaction is *inhibited* by increasing $[lutH^+]/[lut]$ (Fig. 2). This behaviour is consistent with the mechanism shown in Scheme 2. This mechanism is analogous to that shown in Scheme 1, except that the act of substitution is associative, involving attack of PhSH at Fe

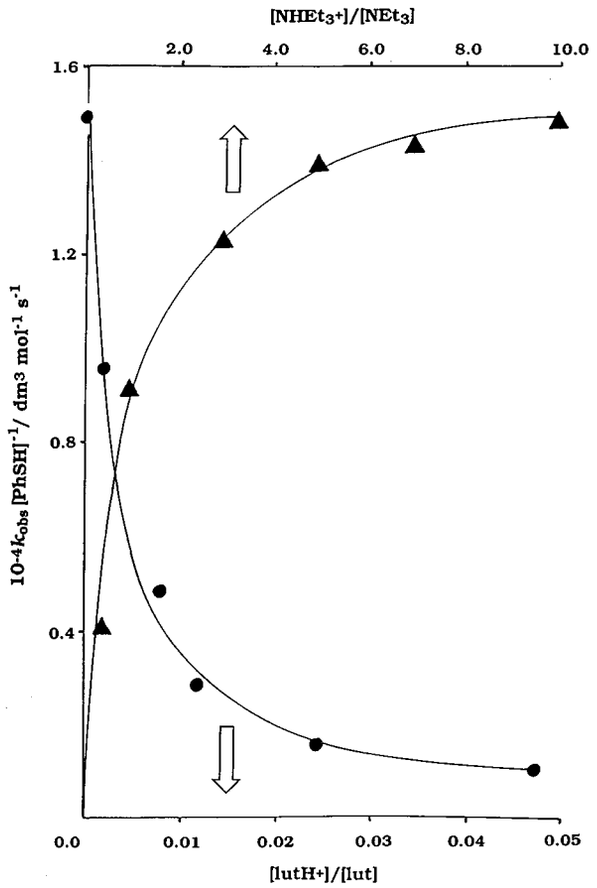


Fig. 2 The kinetics of the first substitution reaction of $[Fe_4S_4Cl_4]^{2-}$ with PhSH, in the presence of acid in MeCN at 25.0 °C. Effect of single protonation (▲): dependence of $k_{obs}/[PhSH]$ on $[NHEt_3^+]/[NEt_3]$. Curve and data from ref. 5. Effect of diprotonation (●): dependence of $k_{obs}/[PhSH]$ on $[lutH^+]/[lut]$. Curve drawn is that defined by equation (5) and the values in the text. For the studies where $[lutH^+]/[lut] < 1.0$, the calculated amount of lut was added to a solution containing $[lutH^+] = 10.0$ mmol dm^{-3} and $[PhS^-] = 5.0$ mmol dm^{-3}

prior to chloride dissociation. The general rate law for this mechanism is shown in equation (4). The only difference

$$\frac{-d[Fe_4S_4]}{dt} = \frac{\{K_1^C k_5^C[lutH^+]/[lut] + K_1^C K_2^C k_6^C[lutH^+]^2/[lut]^2\}[PhSH][Fe_4S_4]}{1 + K_1^C[lutH^+]/[lut] + K_1^C K_2^C[lutH^+]^2/[lut]^2} \quad (4)$$

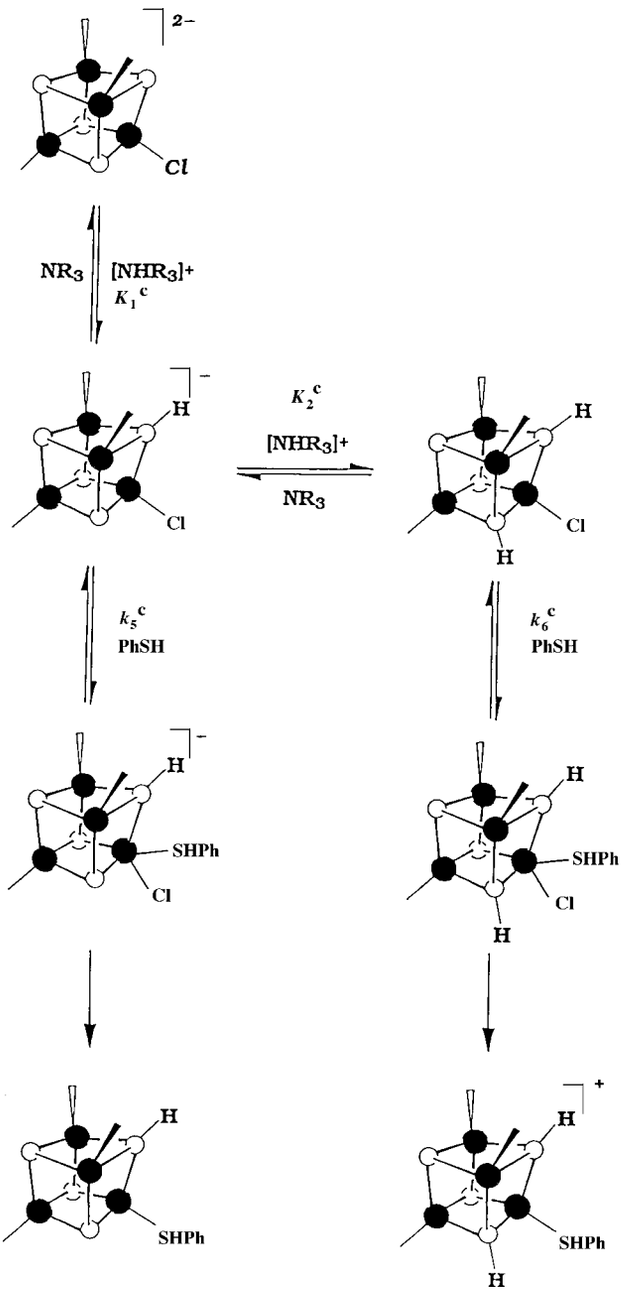
between equations (2) and (4) is the dependence on the concentration of PhSH in the numerator of the latter, consistent with the associative mechanism.

Earlier studies[1] showed that the first protonation of $[Fe_4S_4Cl_4]^{2-}$ is associated with $pK_a = 18.8$.[1] Hence, $K_1^C = 5.0 \times 10^4$ can be calculated and thus, under the conditions studied in this paper, $K_1^C[lutH^+]/[lut] \gg 1$, and equation (4) simplifies to equation (5), with $k_5^C = 1.5 \pm 0.2 \times 10^4$ dm^3 mol^{-1} s^{-1},

$$\frac{-d[Fe_4S_4]}{dt} = \frac{\{k_5^C + K_2^C k_6^C[lutH^+]/[lut]\}[PhSH][Fe_4S_4]}{1 + K_2^C[lutH^+]/[lut]} \quad (5)$$

$k_6^C = 4.0 \pm 0.5 \times 10^2$ dm^3 mol^{-1} s^{-1} and $K_2^C = 3.3 \pm 0.2 \times 10^2$; $pK_a^C = 16.6$. [The value of k_5^C determined in these studies is in excellent agreement with that determined earlier[4] using $[NHEt_3]^+$ ($k_5^C = 1.5 \pm 0.2 \times 10^4$ dm^3 mol^{-1} s^{-1}).]

The dramatically different effects of single and double protonation, on the lability of $[Fe_4S_4Cl_4]^{2-}$ are not a consequence of the two protons binding to different sites. We have already



Scheme 2 Mechanism for the associative acid-catalysed substitution reactions of $[Fe_4S_4Cl_4]^{2-}$ (Fe = ●; S = ○). For clarity, only the Cl group undergoing substitution is shown

shown (with $[NHEt_3]^+$) that protonation of $[Fe_4S_4Cl_4]^{2-}$ occurs exclusively at the cluster core (probably μ_3-S).[4] Even with $[lutH]^+$ protonation of the chloro-ligand is thermodynamically unfavourable ($pK_a^{HCl} = 8.9$).[3] Why successive protonations affect the lability of $[Fe_4S_4Cl_4]^{2-}$ so differently is a consequence of this cluster undergoing substitution by an associative mechanism.

The protonation of μ_3-S residues will have two effects on the reaction. First, protonation will increase the Fe–Cl bond strength (the chloro-ligand is predominantly a σ-donor and weak π-donor or -acceptor). This effect alone would result in a decreased rate of substitution. However, protonation will also decrease the electron density on Fe thus facilitating attack by the PhSH nucleophile. Experimentally, we observed that the nett effect of protonating one μ_3-S is to increase the rate of substitution (Fig. 2). This must be because the dominant effect of single protonation is to facilitate nucleophilic attack. Protonation of two μ_3-S groups will compound these electronic effects. However, the major effect of the second protonation must be to further strengthen the Fe–Cl bond without significantly increasing the rate of nucleophilic attack, resulting in inhibition of the substitution.

Although the behaviour described in this paper is unusual, its mechanistic origins indicate that it may operate in other systems. We have observed that the substitution reactions of $[Fe_4S_4(SEt)_4]^{2-}$ (which reacts by a dissociative mechanism) are catalysed by the addition of one or two protons, whilst those of $[Fe_4S_4Br_4]^{2-}$ and $[\{MoFe_3S_4Cl_3\}_2(\mu\text{-}SPh)_3]^{3-}$ (which react by an associative mechanism) are catalysed by the addition of one proton, but inhibited by the addition of the second proton. Although this paper concerns the reactivity of clusters, in principle, other compounds could show this behavior. It appears that the only requirements are that the species undergoing substitution is capable of binding two protons and that the mechanism of the substitution step is associative.

Acknowledgements

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