# Novel Subsite-Differentiated [4Fe-4S] Clusters Based on Cyclotriveratrylene

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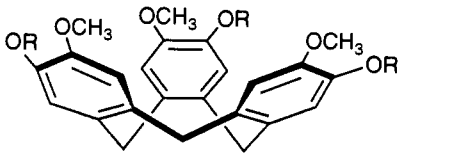
It is known that [4Fe-4S] clusters in certain proteins and enzymes can exhibit special structural or reactivity properties at subsites of the cluster cores.[1] This feature has evoked interest in developing synthetic models that mimic these properties. Holm's group recently described two elegant tripodal ligand systems from which subsite-differentiated [4Fe-4S] clusters can be synthesized.[2] For this purpose Evans used a more accessible trithiol based on triazacyclane.[3] In this communication we present novel subsite-differentiated clusters based on the building block cyclotriveratrylene (CTV). The latter molecule has a rigid, bowllike shape and possesses trifold symmetry.[4] We have provided the CTV framework with ethyl or xylylic arms that are terminated by thiol groups; see ligands **1** and **2** in Figure 1. Reaction of **1** and **2** with $[Fe_4S_4Cl_4]^{2-}$ in the presence of a base or with $[Fe_4S_4(S^tBu)_4]^{2-}$ gives the 3:1 differentiated clusters $[(CTVS_3)Fe_4S_4Cl]^{2-}$ (**3**) and $[(CTVS_3)Fe_4S_4(S^tBu)]^{2-}$ (**4**); see Figure 2. In both compounds the cluster core is partially encapsulated by the ligand, giving rise to structures in which the subsite is either oriented inward (**3**) or outward (**4**).

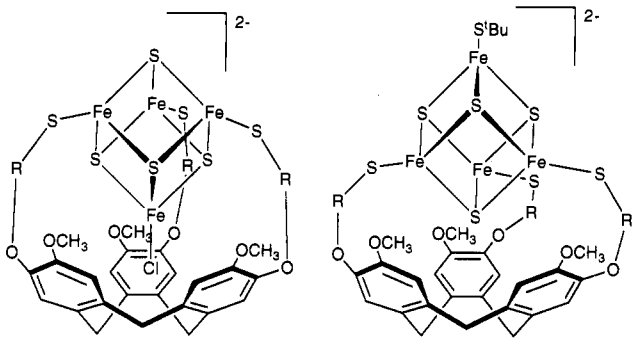
Ligands **1** and **2** were synthesized by alkylating cyclotriguaiacylene with either 1,2-dibromoethane or $\alpha,\alpha'$-dibromo-*m*-xylene. The resulting tribromides were treated with sodium dimethyldithiocarbamate in acetonitrile, and the products were reduced with lithium aluminum hydride in dry and oxygen-free ether. After acidification, the trithiols **1** and **2** were obtained in 22% yield.[5]

Exchange reactions of $(PPh_4)_2[Fe_4S_4Cl_4]$ or $(Bu_4N)_2[Fe_4S_4Cl_4]$ with 1 equiv of **1** or **2** and 3 equiv of $Bu_4NOH$ in dimethylformamide were conducted under a nitrogen atmosphere in very dilute ($10^{-3}$ M) solutions. Upon mixing of the reactants, the color of the reaction mixture immediately changed from purple-brown to yellow-brown. After addition of ether, compounds **3a** and **3b** precipitated as black solids. Cluster compounds **4a** and **4b** were synthesized by treating $[Fe_4S_4(S^tBu)_4]^{2-}$ ($10^{-3}$ M) with 1 equiv of **1** or **2** in dimethylformamide under dynamic vacuum.




CTV(SH)$_3$: **1** R = $CH_2CH_2SH$
**2** R = *m*-$CH_2C_6H_4CH_2SH$

**Figure 1.**




**3a**: R = $CH_2CH_2$
**3b**: R = *m*-$CH_2C_6H_4CH_2$

**4a**: R = $CH_2CH_2$
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**Figure 2.**

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(5) $^1$H NMR for **1** (400 MHz, $CDCl_3$): $\delta$ 1.64 (t, 3H, S*H*, $J$ = 8 Hz), 2.85 (dt, 6H, $CH_2S$, $J$ = 6 Hz, $J$ = 8 Hz), 3.54 (d, 3H, $H_{eq}$, $J$ = 14 Hz), 3.84 (s, 9H, $OCH_3$), 4.10 (t, 6H, $OCH_2$, $J$ = 6 Hz), 4.75 (d, 3H, $H_{ax}$, $J$ = 14 Hz), 6.78 (s, 3H, Ar *H*), 6.82 (s, 3H, Ar *H*). $^{13}$C NMR for **1** ($CDCl_3$): $\delta$ 23.8 ($CH_2S$), 36.4 ($CH_2$), 56.2 ($OCH_3$), 71.5 ($OCH_2$), 113.8 (Ar *C*H), 116.7 (Ar *C*H), 131.8 (Ar *C*$CH_2$), 132.2 (Ar *C*$CH_2$), 146.4 (Ar *C*O), 148.7 (Ar *C*O). Anal. Calcd for $C_{30}H_{36}O_6S_3$ (**1**): C, 61.20; H, 6.16; S, 16.34. Found: C, 61.04; H, 6.19; S, 16.13. FAB-MS for **1**: $m/e$ = 588 ($M^+$). $^1$H NMR for **2** (90 MHz, $CDCl_3$): $\delta$ 1.72 (t, 3H, S*H*), 3.43 (d, 3H, $H_{eq}$), 3.73 (d, 6H, $CH_2S$), 3.72 (s, 9H, $OCH_3$), 4.68 (d, 3H, $H_{ax}$), 5.07 (s, 6H, $OCH_2$), 6.68 (s, 3H, Ar *H*), 6.83 (s, 3H, Ar *H*), 7.27 and 7.34 (m, 12H, Xyl *H*). Anal. Calcd for $C_{48}H_{48}O_6S_3$ (**2**): C, 74.96; H, 6.29; S, 12.51. Found: C, 75.04; H, 6.22; S, 12.32. FAB-MS for **2**: $m/e$ = 816 ($M^+$).

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(7) All compounds showed in the UV–vis (DMF) spectra absorption maxima at ca. 290 nm (50 000 $M^{-1}cm^{-1}$), 300 nm (sh, 25 000 $M^{-1}cm^{-1}$), and 420 nm (15 000 $M^{-1}cm^{-1}$). **3a** $(Bu_4N)_2$: $^1$H NMR (90 MHz, 298 K, [$^2H_6$]DMSO) $\delta$ 0.9 (24 H, $NCH_2CH_2CH_2CH_3$), 1.3 (16H, $NCH_2CH_2CH_2CH_3$), 3.5 (3H, $H_{eq}$), 3.7 (9H, $OCH_3$), 4.1 (6H, $OCH_2$), 4.5 (3H, $H_{ax}$), 7.1 (6H, Ar *H*), 13.5 (br, 6H, $CH_2S$). Anal. Calcd for $C_{62}H_{105}O_6S_7Fe_4N_2Cl$: C, 51.08; H, 7.26; S, 15.39; N, 1.92. Found: C, 50.78; H, 6.57; S, 14.10; N, 1.62. Visual examination showed that the sample was contaminated with iron oxide. **3b** $(Bu_4N)_2$: $^1$H NMR (90 MHz, 298 K, [$^2H_6$]DMSO) $\delta$ 0.9 (24 H, $NCH_2CH_2CH_2CH_3$), 1.3 (16H, $NCH_2CH_2CH_2CH_3$), 1.6 (16H, $NCH_2CH_2CH_2CH_3$), 3.2 (16H, $NCH_2CH_2CH_2CH_3$), 3.4 (3H, $H_{eq}$), 3.7 (9H, $OCH_3$), 4.6 (3H, $H_{ax}$), 5.1 (6H, $OCH_2$), 7.0–7.3 (18 H, Ar *H* and Xyl *H*), 13.8 (6H, $CH_2S$). **4a** $(Bu_4N)_2$: $^1$H NMR (90 MHz, 298 K, [$^2H_6$]DMSO) $\delta$ 0.9 (24H, $NCH_2CH_2CH_2CH_3$), 1.3 (16H, $NCH_2CH_2CH_2CH_3$), 1.6 (16H, $NCH_2CH_2CH_2CH_3$), 2.7 (9H, $SC(CH_3)_3$), 3.2 (16H, $NCH_2CH_2CH_2CH_3$), 3.5 (3H, $H_{eq}$), 3.7 (9H, $OCH_3$), 4.1 (6 H, $OCH_2$), 4.7 (3H, $H_{ax}$), 7.1 (6H, Ar *H*), 13.4 (br, 6H, $CH_2S$). Complex was not isolated. **4b** $(PPh_4)_2$: $^1$H NMR (400 MHz, 298 K, [$^2H_6$]DMSO) $\delta$ 2.7 (9H, $SC(CH_3)_3$), 3.4 (3H, $H_{eq}$), 3.7 (9H, $OCH_3$), 4.7 (3H, $H_{ax}$), 5.3 (6H, $OCH_2$), 7.0–7.2 and 7.3 (18H, Ar *H* and Xyl *H*), 7.6–7.9 (40H, $P(C_6H_5)_4$, 13.5 (6H, $CH_2S$); $^1$H NMR (400 MHz, 330 K, [$^2H_6$]DMSO) $\delta$ 2.8 (9H, $SC(CH_3)_3$), 3.6 (3H, $H_{eq}$), 3.9 (9H, $OCH_3$), 4.7 (3H, $H_{ax}$), 5.2 (6H, $OCH_2$), 6.9–7.1 and 7.4 (18H, Ar *H* and Xyl *H*), 7.6–7.9 (40H, $P(C_6H_5)_4$, 14.3 (6H, $CH_2S$). Anal. Calcd for $C_{100}H_{94}O_6S_8Fe_4P_2$·1.5DMF (from NMR): C, 61.43; H, 5.15; S, 12.55; N, 1.03. Found: C, 57.11; H, 4.59; S, 11.31; N, 0.90. Visual examination showed that the sample was contaminated with iron oxide. Reaction of **4b** with benzoyl chloride: $^1$H NMR (400 MHz, 298 K, [$^2H_6$]DMSO) $\delta$ 3.4 (3H, $H_{eq}$), 3.7 (9H, $OCH_3$), 4.6 (3H, $H_{ax}$), 5.1 (6H, $OCH_2$), 7.0–7.3 (18 H, Ar *H* and Xyl *H*), 7.6–7.9 (40H, $P(C_6H_5)_4$, 13.5 (6H, $CH_2S$). Anal. Calcd for $C_{96}H_{85}O_6S_7Fe_4ClP_2$·1.5DMF (from NMR): C, 60.67; H, 4.84; S, 11.28; N, 1.06; Fe, 11.23. Found: C, 60.65; H, 5.28; S, 11.25; N, 0.96; Fe, 9.22.

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**Table 1.** Electrochemical Properties of the Cluster Compounds[a]

| compd | modulator | $E_{1/2}$/V | $\Delta E_p$/mV | $i_{pa}/i_{pc}$ |
|---|---|---|---|---|
| **3a** | | −1.68 | 60 | 1.0 |
| **3a** | 20 mM $Ba(ClO_4)_2$ | −1.61 | 20 | 1.0 |
| **3b** | | −1.69 | 70 | 1.1 |
| **3b** | 20 mM $Ba(ClO_4)_2$ | −1.62 | 5 | 1.0 |
| **4a** | | −1.80 | 70 | 0.9 |
| **4a** | 20 mM $Ba(ClO_4)_2$ | −1.72 | 10 | 1.0 |
| **4b** | | −1.78 | 80 | 1.0 |
| **4b** | 20 mM $Ba(ClO_4)_2$ | −1.70 | 30 | 1.0 |

[a] 2−/3− reduction at 25 °C in DMF using a pyrolytic graphite working electrode, a Pt auxiliary electrode, an Ag/AgCl reference electrode, and 0.1 mol $dm^{-3}$ tetrabutylammonium hexafluorophosphate as the supporting electrolyte. Potentials are vs $Fc^+/Fc$.

UV–vis spectra in DMF clearly revealed that compounds **3** and **4** were thiolate-ligated $[4Fe\text{-}4S]^{2+}$ clusters. These spectra displayed great similarity to the UV–vis spectra of $[Fe_4S_4(SEt)_4]^{2-}$ and $[Fe_4S_4(SCH_2Ph)_4]^{2-}$.[6] The structural assignment was supported by the observation of temperature-dependent isotropic shifts for the $-CH_2S$ protons in the $^1H$ NMR spectra of **3** and **4**.[7] For example, the $-CH_2S$ signals in cluster **4b** are shifted 10 ppm at 298 K with respect to the free thiol **2** and 10.9 ppm at 330 K, which is in accordance with literature values.[8] As with the macrocyclic [4Fe-4S] cluster compounds of Okuno,[9] there is always some DMF present, as indicated by resonances at 2.72, 2.91, and 7.94 ppm. From the presence of an Fe–Cl vibration at 351 $cm^{-1}$ in the IR spectra of cluster compounds **3**, it was concluded that these compounds still have a chloro ligand. The intensity of the peak was smaller than in the case of the tetrachloro cluster. From differential pulse voltammetry, it was evident that **3** was not contaminated with $[Fe_4S_4Cl_4]^{2-}$. Compound **4b** displayed in the $^{57}Fe$ Mössbauer spectrum (77 K) an absorption with an isomer shift of 0.51 mm/s and a quadrupole splitting of 1.33 mm/s. For compound **3b**, two doublets were observed, one at 0.32 mm/s ($\Delta E_Q$ = 1.15 mm/s) and one at 0.29 mm/s ($\Delta E_Q$ = 0.69 mm/s), their ratio being 3:1. These data are in accordance with data found in the literature for other $[4Fe\text{-}4S]^{2+}$ clusters.[3] In frozen DMSO solutions of **3b** and **4b**, the same results were obtained.

The half-wave potential of the reduction of **3b** was found at −1.69 V (DMF, vs $Fc^{+/0}$), which is between the redox potentials measured for the reduction of $[Fe_4S_4Cl_4]^{2-}$ (−1.35 V) and the reduction of the model complex $[Fe_4S_4(SCH_2C_6H_4CH_2OPh)_4]^{2-}$ (−1.80 V). We used a pyrolytic graphite working electrode to measure the redox potential of **3b** and observed that the current response improved when the number of scans was increased. This so-called self-promotion effect is also known for the electrochemical reduction of certain proteins in water. We also observed a considerable increase in the current response and a decrease of peak separation after addition of $Ba^{2+}$ ions.[10] We believe that without a modulator the cluster complex is oriented with its convex side facing the electrode surface. As a result, electron transfer is hampered. In the presence of a modulator the complex changes orientation due to an inversion of the polarity of the electrode surface and electron transfer becomes possible. As with our previously reported semiencapsulated cluster based on diphenylglucoluril, the redox potential of **3b** shifted 70 mV when $Ba^{2+}$ was added.[11] The optimal current response was found at a $Ba^{2+}$ concentration of about 20 mM. In the presence of $Ba^{2+}$ we still observed a self-promotion effect. With the modulator present the redox reactions are chemically reversible as could be deduced from the anodic to cathodic peak current ratio of 1.0. That these redox reactions are controlled by adsorption was concluded from the linear responses of $i_{pc}$ to the scan rate, the small peak separations, and the increasing current response with increasing number of scans. The half-wave potential of compound **4b** was found at −1.78 V. The current response showed the same electrochemical behavior as that of **3b**. The redox behavior of the clusters with the alkyl spacers (**3a** and **4a**) was very similar to the behavior of the clusters with the xylylic spacers (Table 1).

To investigate whether the unique ligand is pointing toward or away from the cavity of the CTV unit, we performed exchange reactions, which were followed by cyclic voltammetry and $^1H$ NMR spectroscopy. Addition of sodium thiophenolate or sodium dimethyldithiocarbamate to either **3a** or **3b** gave, according to the cyclic voltammogram, no reaction, even when a large excess of reagent was used. Reaction with $OH^-$ gave products with reversible waves at −1.77 and −1.74 V (20 mM $Ba^{2+}$), respectively. Reaction of **4b** with 1 equiv of thiophenol yielded a product with a redox potential of −1.68 V (20 mM $Ba^{2+}$). Reaction with 1 equiv of benzoyl chloride, gave a product which showed a redox potential at −1.63 V (20 mM $Ba^{2+}$). This suggests that in the latter case the 2-methyl-2-propanethiolate group of **4b** is substituted by a chloro ligand. Support for this comes from the disappearance of the *tert*-butyl resonance in the NMR spectrum and the appearance of the Fe–Cl vibration at 351 $cm^{-1}$ in the IR spectrum. In contrast to **3b**, the newly formed chloro complex did react with sodium thiophenolate and sodium dimethyldithiocarbamate to give products with redox potentials of −1.68 V (20 mM $Ba^{2+}$) and −1.75 V (20 mM $Ba^{2+}$), respectively. From this result we may conclude that the chloro ligand is pointing away from the cavity, resulting in a structure that is an isomer of **3b**.

Reaction of **4a** with thiophenol or benzoyl chloride resulted in a mixture of products, indicating that these reactants do not discriminate between the different subsites of **4a**.

From these results we may conclude that reaction of the CTV ligands **1** and **2** with $[Fe_4S_4Cl_4]^{2-}$ gives 1:1 products with the chloro ligands pointing toward the cavity of the CTV units. Apparently, the unique iron is shielded and can only react with small reagents like $OH^-$. Reaction of **1** and **2** with $[Fe_4S_4(S^tBu)_4]^{2-}$ yields compounds with the unique iron outside the cavity, probably because the *tert*-butyl group does not fit into the cavity.

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