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Subsite-Differentiated Analogues of Biological $[4Fe-4S]^{2+}$ Clusters: Synthesis, Solution and Solid-State Structures, and Subsite-Specific Reactions

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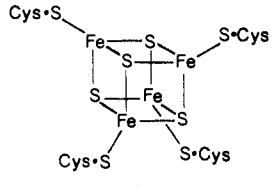
Abstract: Evidence is accumulating that the $Fe_4S_4(SCys)_4$ clusters in certain proteins and enzymes exhibit structural or reactivity features at specific Fe subsites of the $[Fe_4S_4]^{2+,+}$ cluster cores. Synthetic analogues $[Fe_4S_4(SR)_4]^{2-,3-}$ of these clusters possess effectively equivalent Fe subsites and undergo statistical ligand substitution reactions, thereby rendering difficult the purposeful development of corresponding subsite-specific behavior for study at the small molecule level of detail. This problem has been solved for a single differentiated subsite by the synthesis of a semirigid trithiol ligand which readily binds to a single cluster. The approach was based on the cavitand concept as exploited with hexasubstituted benzenes whose conformations frequently correspond to a serial up–down (*a*/*b*) arrangement of large substituents. Ligand design is discussed. The compound 1,3,5-tris((4,6-dimethyl-3-mercaptophenyl)thio)-2,4,6-tris(*p*-tolylthio)benzene (**5**) was prepared from 1,3,5-trifluorobenzene and *m*-xylene in a six-step synthesis. Reaction of **5** with $[Fe_4S_4(SEt)_4]^{2-}$ afforded $[Fe_4S_4(L{\cdot}S_3)(SEt)]^{2-}$ (**7**) which was treated with 1 equiv of pivaloyl chloride to afford $[Fe_4S_4(L{\cdot}S_3)Cl]^{2-}$ (**8**) in 58% yield as its Ph_4P^+ salt. $(Ph_4P)_2$**8** crystallizes in triclinic space group $P\bar{1}$ with a = 13.537 (3) Å, b = 15.099 (4) Å, c = 24.550 (6) Å, α = 94.42 (2)°, β = 92.73 (2)°, γ = 101.84 (2)°, and Z = 2. With use of 7662 unique data ($F_o^2 > 3\sigma(F_o^2)$), the structure was refined to R (R_w) = 5.3 (5.9)%. The anion has the conformation *aaabaa*, with three arms binding the cluster above the central or template benzene ring and two of the three *p*-tolylthio legs on this side of the ring. The differentiated subsite contains a terminal chloride ligand. Cluster dimensions are slightly irregular but within normal ranges. The desired structure was achieved. The following ligand substitution reactions with the indicated reagent were demonstrated by ^1H NMR spectroscopy in acetonitrile solutions: $[Fe_4S_4(L{\cdot}S_3)(SR)]^{2-} \rightarrow$ **8** (*t*-BuCOCl; R = Et, *p*-C_6H_4Br, 2,6-$C_6H_3Cl_2$); **8** $\rightarrow$ $[Fe_4S_4(L{\cdot}S_3)(SR)]^{2-}$ (NaSR; R = Et, *t*-Bu (**10**), *p*-C_6H_4Br); **7** $\rightarrow$ $[Fe_4S_4(L{\cdot}S_3)(SR)]^{2-}$ (RSH; R = *p*-BrC_6H_4, 2,6-$C_6H_3Cl_2$). All reactions are rapid, *regiospecific* at the unique site, and *quantitative*. Further, reaction of cluster **10** with varying equivalents of NaS-*t*-Bu afforded three species: unreacted **10**, the sodium salt of **5**, and $[Fe_4S_4(S\text{-}t\text{-}Bu)_4]^{2-}$ (**15**). The core is removed from the tridentate ligand as **15** or not at all—an "all-or-nothing" reaction indicative of substantial stability of **10** and related cluster anions derived from **5**. ^1H NMR and ^{13}C NMR spectra of clusters are consistent only with trigonal symmetry in solution, consistent with a conformational change of the ligand to *ababab*. In addition to **5** and its triprotected precursor **4**, some six other hexasubstituted benzenes were synthesized by the reaction of the appropriate sodium thiolate with C_6Cl_6 or C_6F_6. Their conformations were further investigated by X-ray diffraction and NMR spectroscopy. A conformational description of hexasubstituted benzenes with X-phenyl substituents (X = O, S, CH_2) has been devised in terms of tilt and cant angles of the phenyl rings relative to the central ring. Compound **4** crystallizes in space group $P\bar{1}$ with the conformation *abbabb*. Similarly, $C_6(SC_6H_4\text{-}2\text{-}Me)_6$ crystallizes in $P\bar{1}$ but with two inequivalent molecules of conformations *bbaaab* and *baabab*. Regardless of their solid-state structures (where known), all hexasubstituted benzenes examined in this work adopt exclusively, by NMR criteria, a minimally trigonally symmetric conformation in solution.

The cubane-type cluster **1** is one of the most widely distributed electron transfer sites in biology. We have shown that clusters containing the core oxidation levels $[Fe_4S_4]^{2+}$ and $[Fe_4S_4]^{+}$ are meaningful synthetic representations of the sites in oxidized and



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reduced ferredoxin (Fd) proteins, respectively, and in a number of enzymes containing these sites.[1] The Fe *sub*sites of biological clusters cannot be exactly equivalent and sometimes small differences between two or more of these subsites are manifested spectroscopically, as in, e.g., the Mössbauer spectra of *Bacillus stearothermophilus* Fd_{red}[2] and *E. coli* sulfite reductase.[3] In these cases, the four Fe atoms are pairwise inequivalent with detectable differences in isomer shifts, quadrupole splittings, and hyperfine coupling constants. The Mössbauer spectra of a number of Fd_{ox} proteins, including that from *B. stearothermophilus*[2] and the *Chromatium* high-potential protein,[4] have been analyzed in terms of two or more slightly inequivalent subsites. In addition, isotropically shifted ^1H NMR spectra of $Fd_{ox,red}$ proteins generally reflect the inequivalence of cysteinyl residues and, therewith, of Fe subsites required by a lack of symmetry of the protein structure. Of particular significance are those cases in which intrinsic subsite inequivalence is accentuated by an electronic, reactivity, or structural feature that is critical to an understanding of cluster structure and function. We have enumerated certain of these cases elsewhere.[5] A leading example is found with aconitase. Reconstitution of the Fe_3S_4 center of the inactive enzyme results in formation of a fully active enzyme containing a Fe_4S_4 cluster.[6] The iron atom added to the Fe_3S_4 cluster becomes a specific subsite in the product cluster, at which a variety of substrates and inhibitors are bound.[7] In its bound form, this subsite is clearly differentiated from the others by its spectroscopic features, which

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suggest five- or six-coordination. Conventionally, biological clusters have the subsite coordination units in **1**. A somewhat similarly distinct subsite exists in the "P-clusters" of nitrogenase, where one has properties indicative of a localized Fe^{2+} atom in a sulfur ligand environment.[8] Reconstitution of the Fe_3S_4 site in dithionite-reduced *D. gigas* Fd II with Fe(II) builds a Fe_4S_4 cluster, in which the added Fe atom occupies one (at most two) subsite(s).[9] It is highly probable that in the apparent MFe_3S_4 clusters formed upon incubation of Fd II with Co(II)[10] or Zn(II),[11] the heterometal resides in the same site as added Fe(II). Further, it is entirely likely that the subsite vacancy created in the oxidative process $Fe_4S_4 \rightarrow Fe_3S_4$ is that which is occupied in reconstitution, assuming the latter cluster has an imperfect cubane structure such as has been proposed by ourselves[12] and others[13] on the basis of magnetic and spectroscopic evidence. The siroheme prosthetic group in *E. coli* sulfite reductase has been found by crystallography to be coupled to a Fe_4S_4 cluster by means of a bridging cysteinyl sulfur atom which is an axial ligand of the heme Fe atom.[14] Given their similarities, it would not be surprising if the catalytic sites of most or all assimilatory sulfite and nitrite reductases were not configured in this way.

The foregoing observations make evident the desirability of a Fe_4S_4 cluster so designed as to facilitate the investigation of *subsite-specific* phenomena, particularly as related to biological structure and function. Cluster **1** in either oxidation level does not lend itself to this task inasmuch as the subsites are essentially independent. Thus, ligand substitution reactions afford statistical product distributions,[15,16] in keeping with the 6–7-Å separation of terminal ligand atoms and the virtual or required equivalence of Fe subsites in crystalline solids.[1] In the solid state, it has been possible on occasion to differentiate subsites. The Et_4N^+ salt of $[Fe_4S_4(SC_6H_4\text{-}2\text{-}(OH))_4]^{2-}$ crystallizes with one five-coordinate subsite owing to coordination of the hydroxyl group, but all subsites become four-coordinate and therefore equivalent in solution.[17] Several mixed-ligand clusters have been crystallized and their existence proven in the solid state by X-ray diffraction.[18,19] Our experience with several of these clusters when examined by high-field NMR is that they disproportionate to essentially statistical mixtures, a possibility recognized by Kanatzidis et al.[19]

These findings show that deliberate manipulation of a single subsite requires a suitably designed polydentate ligand system that differentiates subsites in a 3:1 ratio. This article reports the initial accomplishment of this goal by means of a semirigid tridentate ligand. Ligand and cluster syntheses are described, together with structures in the crystalline and solution states and demonstrations of site-specific reactions. As will be seen, these serve as a basis for investigations of biologically relevant reactions and structures.

Experimental Section

Preparation of Compounds. All operations and manipulations were performed under a pure dinitrogen atmosphere. Solvents were freshly degassed prior to use. FAB mass spectra were taken in 3-nitrobenzyl alcohol. Melting points are uncorrected.

(a) 1,3,5-Trifluoro-2,4,6-tris(*p*-tolylthio)benzene (2). A slurry of 48.5 g (260 mmol) of *p*-tolylthiocuprate[20] and 21.3 g (58.1 mmol) of 1,3,5-trifluoro-2,4,6-tribromobenzene[21] in 500 mL of DMF was maintained at 140 °C for 36 h. The mixture was poured into 250 mL of 12 N HCl and 1500 g of ice and extracted three times with ether (total 1 L, each extract filtered through a glass wool plug). The combined filtrates were washed twice with 10% aqueous K_2CO_3 and once with saturated aqueous NaCl and dried over Na_2SO_4. Removal of ether gave a yellowish-white solid, recrystallization of which from 9:1 hexanes/$CHCl_3$ (v/v) afforded 16.0 g (56%) of pure product as a fluffy white solid; mp 126.5–128 °C. ^1H NMR ($CDCl_3$): δ 2.31 (3, Me), 7.06 (d, 2), 7.20 (d, 2); ^{13}C NMR ($CDCl_3$): δ 108.8–109.2 (m), 163.9 (d/t, J^1_{CF} = 250 Hz, J^3_{CF} = 6 Hz), central ring; 20.98 (Me), 128.8, 129.9, 130.4, 137.5, *p*-tolyl. FAB-MS: 498 (M^+). Anal. Calcd for $C_{27}H_{21}F_3S_3$: C, 64.04; H, 4.25; S, 19.29; F, 11.43. Found: C, 65.35; H, 4.46; S, 19.42; F, 10.91.

(b) 4,6-Dimethyl-3-(methoxymethylthio)benzenethiol (3). DMF (350 mL) was added to 12.3 g (256 mmol) of NaH (50% oil suspension) from which the oil was removed with dry hexane. To this stirred slurry was added 20.7 g (122 mmol) of 1,3-dimercapto-4,6-dimethylbenzene[22] in 150 mL of DMF at a rate such that the temperature of the reaction mixture did not exceed 50 °C. After a minimum of 3 h of stirring, 21.6 g (268 mmol) of chloromethyl methyl ether was added similarly. After a further 6 h, 10.3 g (123 mmol) of NaSEt was added as a solid, and the mixture was heated to 120 °C for ~3 h. The byproduct $EtSCH_2OMe$ was collected in a liquid nitrogen trap. DMF was removed by distillation at ambient pressure leaving a reddish oil, which was dissolved in ether. Multiple extractions with 5% aqueous NaOH, immediate acidification with 2 M HOAc, extractions into ether, and drying of the combined extracts (Na_2SO_4) followed by solvent removal gave 24 g of the crude monoprotected dithiol as a red oil. This material was passed rapidly through a silica plug in toluene to give a yellow oil. Column chromatography (multiple passes) of this oil on 63–200 mesh silica with 50:50 toluene/hexanes (v/v) gave 17.6 g (67%) of the monoprotected thiol. ^1H NMR ($CDCl_3$): δ 2.27 (3, Me), 2.32 (3, Me), 3.27 (1, SH), 3.43 (3, OMe), 4.91 (2, CH_2), 6.98 (1), 7.46 (1). FAB-MS (neat): 214 (M^+).

(c) 1,3,5-Tris(4,6-dimethyl-3-(methoxymethylthio)phenylthio)-2,4,6-tris(*p*-tolylthio)benzene (4). To a slurry of 0.89 g (37 mmol) of dry NaH in 200 mL of THF was added 7.25 g (33.9 mmol) of **3**. After dihydrogen evolution subsided, the solvent was removed in vacuo. The gummy residue was dissolved in 35 mL of 1,3-dimethyl-2-imidazolidinone (DMEU), and 4.33 g (8.70 mmol) of **2** was added rapidly. The solution slowly changed to a red-orange color upon the application of heat. The reaction mixture was stirred for 4 days at 85 °C. Most of the DMEU was distilled off in vacuo, and the residue was dissolved in ether and poured into a 10% K_2CO_3 solution. The aqueous phase was extracted with ether. The organic layer was washed with 10% K_2CO_3 and saturated sodium chloride solution and dried (Na_2SO_4). Column chromatography on 63–200 mesh silica with toluene gave 6.6 g of crude product, recrystallization of which from 1:4 ethyl acetate:hexanes (v/v) afforded 4.0 g of improved purity. Chromatography as in a preceding step gave 3.8 g (41%) of pure product as a yellow solid; mp 115–118 °C. ^1H NMR ($CDCl_3$): δ 2.13 (3, Me), 2.23 (3, Me), 2.27 (3, Me), 3.31 (3, OMe), 4.73 (2, CH_2), 6.83 (s, 1), 6.85 (d, 2), 6.87 (s, 1), 6.89 (d, 2). ^{13}C NMR: δ 147.2, 148.6 (central ring). FAB-MS: 1080 (M^+). Anal. Calcd for $C_{57}H_{60}O_3S_9$: C, 63.29; H, 5.59; S, 26.68. Found: C, 63.08; H, 5.35; S, 27.38. This compound forms an inclusion compound with acetone; the solvate molecules can be removed by heating at 60 °C in vacuo.

(d) 1,3,5-Tris(4,6-dimethyl-3-mercaptophenylthio)-2,4,6-tris(*p*-tolylthio)benzene (5, L-(SH)$_3$). In 500 mL of acetonitrile 1.85 g (1.71 mmol) of **4** was dissolved with heating. After the solution was cooled to 25 °C, 40 mL of absolute ethanol was introduced. Addition of 2.50 g (7.85 mmol) of $Hg(OAc)_2$ gave a cloudy solution after several minutes. After 16 h the solvent was removed in vacuo at ~25 °C. The yellow solid residue was suspended in a 4:1 $CHCl_3$/HOAc solution (v/v) and H_2S

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Table I. Summary of Crystal Data, Intensity Collections, and Structure Refinement Parameters for C_6(S-2-MeC_6H_4)$_6$ (**6**), C_6[1,3,5-(S-3-$MeOCH_2$S-4,6-$Me_2C_6H_2$)$_3$-2,4,6-(S-4-MeC_6H_4)$_3$]·Me_2CO (**4**), and $(PPh_4)_2[Fe_4S_4(L{\cdot}S_3)Cl]$ (**8**)

	6	**4**	**8**
formula	$C_{48}H_{42}S_6$	$C_{60}H_{66}S_9O_4$	$C_{99}H_{85}S_{13}Fe_4P_2Cl$
mol wt	811.2	1139.8	2012.3
a (Å)	12.483 (2)	12.786 (13)	13.537 (3)
b (Å)	15.095 (3)	14.218 (8)	15.099 (4)
c (Å)	21.867 (4)	18.450 (11)	24.550 (6)
α (deg)	92.96 (2)	87.89 (5)	94.42 (2)
β (deg)	98.24 (2)	84.94 (6)	92.73 (2)
γ (deg)	91.74 (2)	64.38 (6)	101.84 (2)
crystal system	triclinic	triclinic	triclinic
Z	4	2	2
V (Å^3)	4069 (1)	3012 (4)	4886 (1)
d_{obsd} (d_{calcd}) (g/cm^3)	1.314 (1.324)	1.250 (1.257)	1.361 (1.368)
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
crystal dimns (mm)	0.60 × 0.30 × 0.18	0.60 × 0.40 × 0.30	0.36 × 0.28 × 0.40
radiation	Mo Kα (λ = 0.71069)	Mo Kα (λ = 0.71069)	Mo Kα (λ = 0.71069)
abs coeff, μ (cm^{-1})	3.6	3.6	9.5
scan speed (deg/min)	2.0–29.3 (ω scan)	2.0–29.3 (ω scan)	2.0–29.3 (2θ scan)
scan range (deg)	0.6 below Kα_1 to 0.6 above Kα_2	0.6 below Kα_1 to 0.6 above Kα_2	0.9 below Kα_1 to 0.9 above Kα_2
backgrd/scan time ratio	0.25	0.25	0.25
2θ limits	$3° \le 2\theta \le 46°$	$4° \le 2\theta \le 50°$	$4° \le 2\theta \le 45°$
data collected	13504 ($+h,\pm k,\pm l$)	11306 ($+h,\pm k,\pm l$)	14488 ($+h,\pm k,\pm l$)
unique data ($F_o^2 > n\sigma(F_o^2)$)	6480 (n = 2.0)	4747 (n = 2.5)	7662 (n = 3.0)
no. of constraints	252	156	272
no. of variables	976	592	1073
R (R_w),[b] %	5.83 (4.39)[c]	7.73 (7.13)[c]	5.3 (5.9)[d]

[a] Determined by the neutral buoyancy in CCl_4/heptane. [b] $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o|^2 - |F_c|^2)/\sum w|F_o|^2]^{1/2}$. [c] Weighting scheme for least-squares refinement: $w = 1/(\sigma^2)$. [d] Weighting scheme for least-squares refinement—3-term Chebyshev (30.53, 42.48, 16.79): Carruthers, J. R.; Watkin, D. J. *Acta Crystallogr.* **1979**, *A35*, 698.

was passed through for ~20 min. The black mixture was transferred to a tightly packed Celite plug on a glass frit and was filtered. The black residue was washed with hot $CHCl_3$ until the washings were colorless (~750 mL). The filtrate and washings were combined and solvents were removed in vacuo. The solid yellow residue was washed with hot acetonitrile and dried in vacuo to yield 1.56 g (97%) of the pure trithiol; mp >203 °C (diffuse). ^{1}H NMR ($CDCl_3$): δ 2.17–2.18 (6, 2 Me), 2.27 (3, Me), 3.07 (1, SH), 6.45 (s, 1), 6.83 (s, 1), 6.84 (d, 2), 6.96 (d, 2). ^{13}C NMR ($CDCl_3$): δ 147.4, 149.3 (central ring). FAB–MS: 948 (M^+).

(e) **Hexasubstituted Benzenes.** These compounds were prepared to test the generality of the synthetic method with a view toward potential hexadentate ligands, and in one case (**6**) to obtain a desired crystal structure. The procedure for $C_6(SC_6H_4$-4-OMe$)_6$ is given as an example and applies to the other compounds below; it is based on that of MacNicol et al.[23] but is more explicit. Either C_6F_6 or C_6Cl_6 may be employed; shorter reaction times may generally be used with the former. Spectroscopic data sufficient for compound identification are given; ^{13}C NMR data are confined to chemical shifts of central ring atoms. Several representative compounds were analyzed.

C_6(SC_6H_4-4-OMe)$_6$. To a solution of 2.60 g (15.8 mmol) of NaSC_6H_4-4-OMe in DMEU was added 0.38 g (1.33 mmol) of C_6Cl_6. The solution assumed a yellow color immediately and heat was evolved. The reaction mixture was stirred at ambient temperature for 4–5 days and was monitored by TLC. If this indicated that reaction was not substantially complete, the mixture was heated to 80–110 °C for an additional 1–4 days. The reaction mixture at this point was diluted with ~200 mL of ether or dichloromethane and poured into water. The aqueous phase was exhaustively extracted with ether or dichloromethane to separate the yellow product. The organic phase was washed with 5% NaOH and saturated aqueous NaCl solution and dried (Na_2SO_4). Solvent was removed to leave a yellowish gummy residue. (Dichloromethane extracts contained DMEU, which was removed by vacuum distillation.) This material was triturated in hot ethanol, resulting in the separation of 1.16 g (96%) of pure product as a yellow solid; mp 161–163 °C. In several cases below, purification of the crude product was achieved by column chromatography (dichloromethane/hexanes or toluene/hexanes eluent) or recrystallization. ^{1}H NMR (acetone-d_6): δ 3.77 (3, Me), 6.78 (d, 2), 6.94 (d, 2). ^{13}C NMR ($CDCl_3$): δ 148.0. FAB–MS: 906 (M^+).

C_6(SC_6H_4-3-OMe)$_6$: 85%; mp 141–144 °C. ^{1}H NMR ($CDCl_3$): δ 3.69 (3, Me), 6.51 (d, 1), 6.52 (d, 1), 6.63 (d, 1), 7.04 (t, 1). ^{13}C NMR ($CDCl_3$): δ 149.5. FAB–MS: 906 (M^+). Anal. Calcd for $C_{48}H_{42}O_6S_6$: C, 63.55; H, 4.67; S, 21.20. Found: C, 63.16; H, 4.89; S, 21.03.

C_6(SC_6H_4-4-OH)$_6$: 90%; mp >252 °C (diffuse). ^{1}H NMR (acetone-d_6): δ 6.72 (d, 2 H), 6.86 (d, 2 H), 8.45 (1, SH). ^{13}C NMR (acetone-d_6): δ 148.0. FAB–MS: 822 (M^+).

C_6(S-2-MeC_6H_4)$_6$ (6): 92%; mp 186–190 °C. ^{1}H NMR (CD_2Cl_2): δ 2.20 (3, Me), 6.65 (d, 1), 6.96 (t, 1), 7.03 (t, 1), 7.08 (d, 1). ^{13}C NMR (CD_2Cl_2): δ 148.9. FAB–MS: 810 (M^+). Anal. Calcd for $C_{48}H_{42}S_6$: C, 71.07; H, 5.22; S, 23.71. Found: C, 70.27; H, 5.48; S, 23.85.

C_6(SC_6H_4-4-SCH_2OMe)$_6$: 82%; mp 137–141 °C. ^{1}H NMR ($CDCl_3$): δ 3.43 (3, Me), 4.93 (2, CH_2), 6.82 (d, 2), 7.24 (d, 2). ^{13}C NMR ($CDCl_3$): δ 148.0. FAB–MS: 1182 (M^+). 1,4-$HSC_6H_4SCH_2OMe$: 1,4-Dimercaptobenzene was prepared from 1,4-$C_6H_4Br_2$ with sodium metal and NaS-*i*-Pr in *N*,*N*-dimethylacetamide.[24] The dithiol was monoprotected in a similar manner to that described for **3**. Two distillations at 175–179 °C/35 Torr and chromatography as with **3** gave the pure monothiol as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.17 (3, Me), 3.42 (1, SH), 4.91 (2, CH_2), 7.20 (d, 2), 7.35 (d, 2).

C_6(SC_6H_4-4-SH)$_6$. The preceding compound was deprotected as described for **4** except that 9 equiv of $Hg(OAc)_2$ were used: 50%; mp >175 °C (diffuse). ^{1}H NMR ($CDCl_3$): δ 3.42 (1, SH), 6.72 (d, 2), 7.05 (d, 2). ^{13}C NMR: δ 147.9. FAB–MS: 918 (M^+). Anal. Calcd for $C_{42}H_{30}S_{12}$: C, 54.86; H, 3.29. Found: C, 54.33; H, 3.41.

$(Ph_4P)_2[Fe_4S_4(L{\cdot}S_3)Cl]$ (8). A solution or slurry of 0.330 g (0.348 mmol) of **5** in 30 mL of DMF was prepared by gentle heating. To this mixture was added an equimolar quantity (0.444 g) of solid $(Ph_4P)_2[Fe_4S_4(SEt)_4]$.[25] The reaction mixture was stirred under dynamic vacuum for 3 h. The ^{1}H NMR spectrum of the solid isolated from a small aliquot of the reaction mixture showed the major cluster product to be $[Fe_4S_4(L{\cdot}S_3)(SEt)]^{2-}$ (**7**). Pivaloyl chloride (0.042 g, 0.348 mmol) was added to the mixture and stirring was continued for 4 h. Ether (~50 mL) was layered on top of the reaction mixture, causing after 1 day formation of an oily material. The solution was decanted away from the oil and 50 mL of ether was added to the removed solution. After 1 day, black crystalline material had formed. This was collected, washed with acetonitrile, and dried in vacuo to yield 0.245 g (35%) of product. Similar treatment of the filtrate gave another 0.160 g, for a 58% total yield of product as a black crystalline solid. The compound was not analyzed but was unambiguously identified by crystallographic, spectroscopic, and electrochemical properties that are described in the text. In separate experiments, cluster **7** as its Ph_4P^+ salt was isolated and purified by recrystallization from acetonitrile. Spectroscopic data identifying this compound are presented below.

(23) MacNicol, D. D.; Mallinson, P. R.; Murphy, A.; Sym, G. J. *Tetrahedron Lett.* **1982**, *23*, 4131.

(24) Testaferri, L.; Tiecco, M.; Tingoli; Chianelli, D.; Montanucci, M. *Synthesis* **1983**, 751.

(25) Averill, B. A.; Herskovitz, T.; Holm, R. H.; Ibers, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 3523.

Collection and Reduction of X-ray Data. Black crystals of cluster compound **8** were grown by vapor diffusion of ether into a DMF solution. The protected ligand compound **4** was crystallized from acetone and obtained as a monosolvate. Crystals of the hexakis compound **6** were obtained by slow evaporation of a dichloromethane solution. Single crystals were mounted in glass capillaries, which were sealed under a dinitrogen atmosphere. Diffraction data were collected at room temperature on a Nicolet P3F four-circle automated diffractometer with use of graphite-monochromatized Mo Kα radiation. Unit cell parameters and orientation matrices were obtained for 25 strong, machine-centered reflections ($20° < 2\theta < 25°$). Data collection and crystal parameters are provided in Table I. Three check reflections monitored every 123 reflections exhibited no significant decay over the course of the data collections. Lorentz and polarization corrections were applied with the program XTAPE of the SHELXTL program package (Nicolet XRD Corp., Madison, WI), and an empirical absorption correction (PSICOR) was applied only to **8**. Axial photographs of the three compounds revealed no symmetry, and simple E statistics favored the centrosymmetric space group $P\bar{1}$ (no. 2) in each case. Density measurements in conjunction with volume calculations suggested $Z = 2$ for **4** and **8** and $Z = 4$ for **6**. Successful refinements of the structures proved these choices to be correct.

Solution and Refinement of Structures. Atom scattering factors were taken from the tabulations of Cromer and Waber.[26] Minimally, the heavy atoms of cluster **8** and the six sulfur atoms bonded to the central ring of **4** and **6** were located by direct methods (MULTAN) with use of random groups. All remaining non-hydrogen atoms of **6** and **8** were found with use of Fourier maps. For **4**, alternating cycles of Fourier maps and least-squares refinements were required to locate portions of two of the three methoxymethyl groups and the acetone solvate molecule because of their large thermal parameters. The disorder was not successfully modeled. All structures were refined using CRYSTALS, where phenyl rings were treated as semirigid bodies except for the central, template ring (ring 0), and the methoxymethyl groups and solvate molecule of **4** were constrained by the method of additional observational equations.[27] Isotropic refinements of all non-hydrogen atoms converged at R = 12.7% (**4**), 9.5% (**6**), and 10.2% (**8**).

In further refinements, all non-hydrogen atoms were described anisotropically except for those of the methoxymethyl groups and the solvate molecule of **4**. With the exception of these portions of **4**, hydrogen atoms were included at 0.96 Å from, and with isotropic thermal parameters 1.2× those of, bonded carbon atoms. The final difference map of **8** shows two peaks of ca. 1.1 e$^-$/Å^3 and no other peaks >0.4 e$^-$/Å^3. For **4**, the final difference map showed no peak >0.6 e$^-$/Å^3 and most of the residual electron density located at or near the methoxymethyl group and the acetone solvate molecule. For **6**, the final map showed no peak >0.4 e$^-$/Å^3. The final R values and weighting schemes used are given in Table I.[28]

Other Physical Measurements. All manipulations and measurements of compounds **5**, **7**, and **8** were carried out under anaerobic conditions. Absorption spectra were recorded on a Cary 219 spectrophotometer. FAB mass spectra were measured on a Kratos MS50 spectrometer equipped with a xenon gun. Electrochemical measurements were performed with standard PAR instrumentation using a Pt working electrode, DMF solvent, and 0.2 M (n-Bu_4N)(ClO_4) supporting electrolyte. Potentials are referenced to a SCE. NMR spectra were determined on a Bruker AM-500 spectrometer. ^{1}H spectra were obtained at 500 MHz and ^{13}C spectra at 125.8 MHz; chemical shifts of both nuclei are relative to Me_4Si internal reference.

Results and Discussion

Tridentate Ligand Design and Synthesis. We have sought a semirigid tridentate ligand with thiol functionalities capable of binding a cubane-type Fe_4S_4[1] and also a heterometal MFe_3S_4 core unit (M = Mo, W;[29] V[30]) in a fit well-matched to cluster dimensions. The experiments of Cram and co-workers[31,32] showing that proper preorganization of cavities in "cavitand" molecules leads to stronger binding between host and guest is pertinent here.

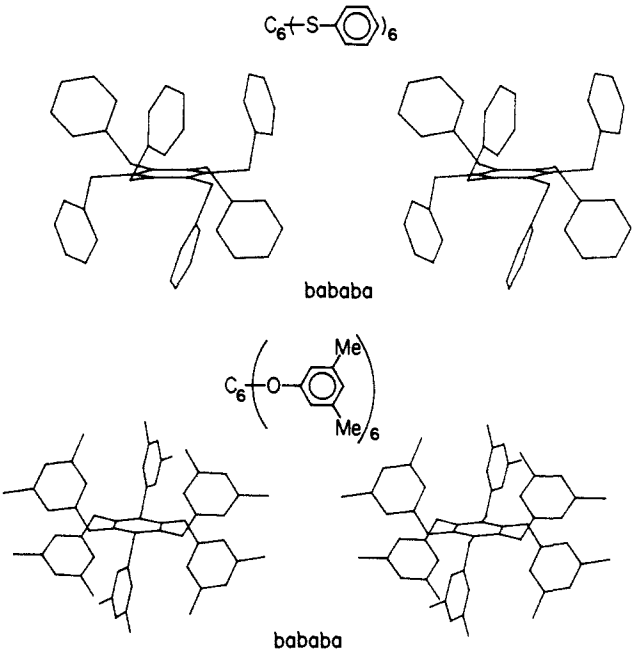
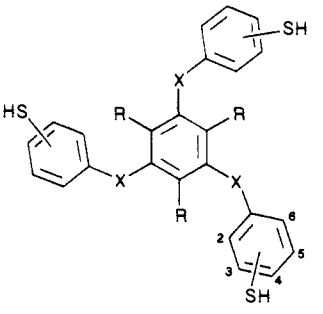


Figure 1. Stereoviews of the structures of $C_6(SPh)_6$[20] and one of the inequivalent molecules of $C_6(O\text{-}3,5\text{-}Me_2C_6H_3)_6$[35] showing their *bababa* conformations.

These results imply that, in addition to proper dimensions for binding the preceding units, the ligand should be predisposed to its binding configuration before cluster formation. In this way, unexpected or unwanted modes of cluster binding and polymerization through bridging interactions, an altogether common occurrence in metal–thiolate complexes,[33] should be avoidable.

Modeling studies indicated that the tripodal molecule **9** was dimensionally appropriate for binding the Fe_4S_4 and other core units. Our interest was drawn to the work of MacNicol and co-workers,[34] who have prepared and structurally characterized a number of hexasubstituted benzenes with six identical substituents. The structures of two of these[20,35] redrawn as stereoviews



9: X = O, S, CH_2

from atom coordinates are shown in Figure 1. Both possess a conformation in which substituent groups alternate in positions below and above the plane of the central ring. In current nomenclature,[36] the conformation is *bababa*. The methyl group locations immediately suggest appropriate positions for the introduction of ligating atoms. At the beginning of this study, this desirable conformation had been established crystallographically for a number of hexasubstituted benzenes with substituents containing phenyl[20,25] (X = O, S) and aliphatic[37] portions. Indeed,

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(27) Waser, J. *Acta Crystallogr.* **1963**, *16*, 1091.
(28) See paragraph at the end of this article concerning supplementary material.
(29) Holm, R. H.; Simhon, E. D. In *Molybdenum Enzymes*; Spiro, T. G., Ed.; Wiley-Interscience: New York, 1985; Chapter 1.
(30) Kovacs, J. A.; Holm, R. H. *Inorg. Chem.* **1987**, *26*, 702, 711.
(31) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.
(32) Cram, D. J. *Science* **1983**, *219*, 1177.
(33) (a) Dance, I. G. *Polyhedron* **1986**, *5*, 1037. (b) Blower, P. J.; Dilworth, J. R. *Coord. Chem. Rev.* **1987**, *76*, 121.
(34) MacNicol, D. D. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Ed.; Academic: New York, 1984; Vol. 2, Chapter 5.
(35) Gilmore, C. J.; MacNicol, D. D.; Murphy, A.; Russell, M. A. *Tetrahedron Lett.* **1983**, *23*, 3269.
(36) MacNicol, D. D.; Mallinson, P. R.; Robertson, C. D. *J. Chem. Soc., Chem. Commun.* **1985**, 1649.

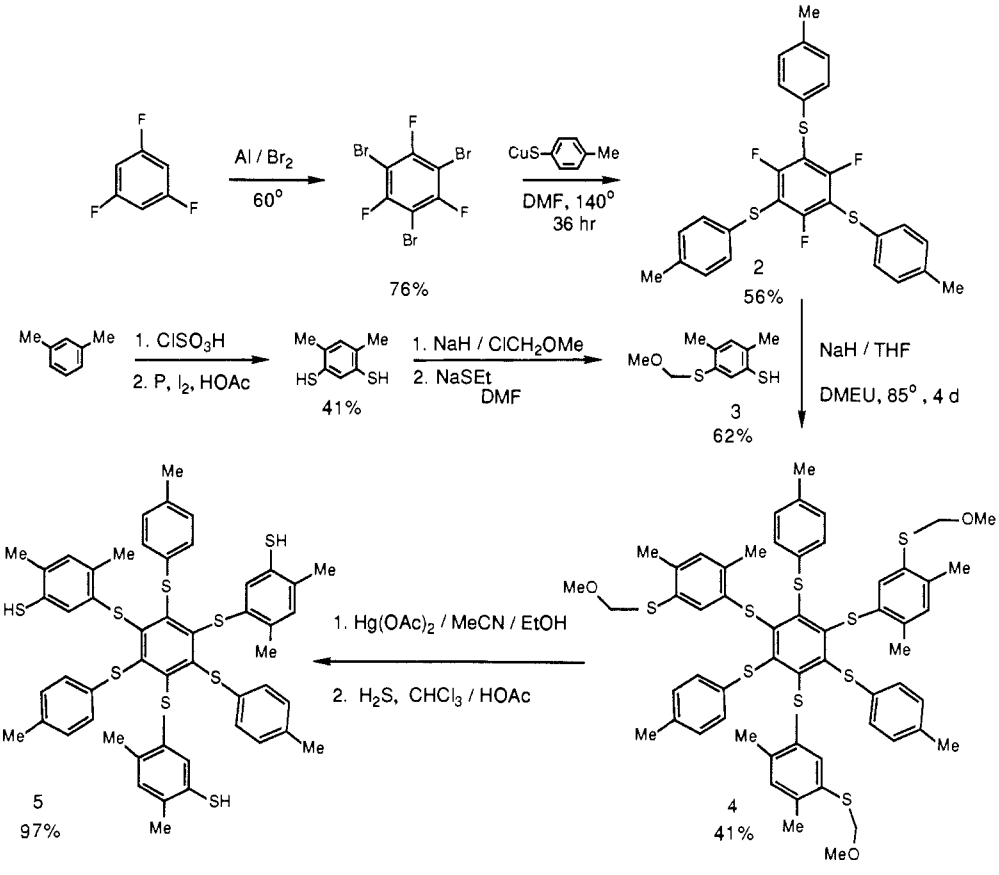

Figure 2. Synthesis of semirigid trithiol ligand **5** starting from 1,3,5-trifluorobenzene and *m*-xylene.

with only one exception, C_6(S-2-naphthyl)$_6$,[23] this stereochemistry, having idealized trigonal symmetry, was adopted by all compounds of known structure in the solid state.

In elaborating **9** to an acceptable ligand, several features require brief consideration. Linking atom X in the coordinating substituents, or "arms", and in the remaining substituents R, or "legs", was chosen as sulfur for convenience in synthesis. On the basis of the results in Figure 1, these substituents are sterically effective in setting the serial up–down arrangement. Placement of the thiol groups at position 3 instead of 4 in the phenyl groups of the arms allows a somewhat more relaxed *complexed* configuration yet one which is semirigid, and defines a cavity whose floor is the central benzene ring and whose walls are the inward edges of the phenyl groups. The 4-thiol ligand should be capable of binding the cubane cores, but it provides more of a platform and less of a cavity mode of cluster positioning, with the possibility that the ligand might not necessarily act as tridentate to a single cluster. Methyl substitution at position 6 (ortho to the linking atom) of the arms should cause the phenyl rings to orient with the 3-thiol groups directed inward toward, rather than away from, the central ring. The latter arrangement would be disfavored by methyl–methyl or methyl–π-electron interactions over the central ring. The desired substitution was most easily accomplished synthetically in terms of the 4,6-dimethyl pattern.

The synthesis of a hexakis(arylthio)benzene with different substituents has not been reported previously. The scheme used here is outlined in Figure 2 and starts with 1,3,5-trifluorobenzene and *m*-xylene. A key step is the selective displacement of aryl bromide in the presence of aryl fluoride by *p*-tolylthiocuprate, as shown earlier by Belf et al.[38] and later by Johnston and Peach,[39] yielding **2** (56%). Coupling of the monoprotected thiol **3** with **2** in DMEU solution by the procedure of MacNicol et al.[23] afforded the fully protected trithiol **4** (41%, unoptimized). Deprotection of **4** by $Hg(OAc)_2/H_2S$ yielded the trithiol ligand L-$(SH)_3$ (**5**, 97%).

Conformational Descriptions of Hexasubstituted Benzenes. Inasmuch as the conformations of these molecules, including **4**, **5**, **6**, **8** and others, are a central issue in this research, an effective means of describing the precise spatial orientation of substituents is required. The *a*/*b* nomenclature for arms and legs "above" and "below" the plane of the central ring, hereafter ring 0, was introduced by MacNicol et al.[36] This is adopted here; when the substituents are numbered, the gross conformation is described by this notation starting in serial order with substituent 1. The choice of *a* or *b* for ring 1 is arbitrary. The description that follows is readily generalized, but it is illustrated with and applied to molecules of the type $C_6(XPh)_6$ (X = O, S), where the substituents XPh are not necessarily identical. Actual conformations of individual substituents (and thus of a molecule) are uniquely defined by two dihedral angles relative to a *reference configuration*, as presented in Figure 3. This configuration is defined by placement of a right-handed coordinate system at each carbon atom of ring 0 such that the $+x$ axis lies along the C–X bond vector and the $+z$ axis is as nearly perpendicular to the plane of ring 0 as the actual structure permits. A substituent is positioned in the plane of the $(+x,+y)$ quadrant such that the carbon atom of lowest substituent number according to standard nomenclature is nearest the origin. The dihedral angles θ and ϕ describe the tilt and cant, respectively, of each substituent relative to the central ring. When viewed down the X–C(0) bond of ring 0, rotation by an angle θ brings the substituent into a position that is described as the tilt. The cant of a substituent is achieved by a rotation ϕ around the C(1)–X bond. These angles are defined under the Klyne-Prelog sign convention: when looking from atom B to atom C in the

(37) (a) Hardy, A. D. U.; MacNicol, D. D.; Swanson, S.; Wilson, D. R. *J. Chem. Soc., Perkin Trans. II* **1980**, 999. (b) Freer, A.; Gilmore, C. J.; MacNicol, D. D.; Wilson, D. R. *Tetrahedron Lett.* **1980**, *21*, 1159. (c) Freer, A.; Gilmore, C. J.; MacNicol, D. D.; Swanson, S. *Tetrahedron Lett.* **1980**, *21*, 205. (d) Burns, K.; Gilmore, C. J.; Mallinson, P. R.; MacNicol, D. D.; Swanson, S. *J. Chem. Res. (M)* **1981**, 0501; *J. Chem. Res. (S)* **1981**, 30. (e) Freer, A. A.; Gall, J. H.; MacNicol, D. D. *J. Chem. Soc., Chem. Commun.* **1982**, 674. (f) See also: Peach, M. E.; Burschka, C. *Can. J. Chem.* **1982**, *60*, 2029.

(38) Belf, L. J.; Buxton, M. W.; Fuller, G. *J. Chem. Soc.* **1965**, 3372.
(39) Johnston, L. J.; Peach, M. E. *J. Fluorine Chem.* **1973**, *12*, 41.

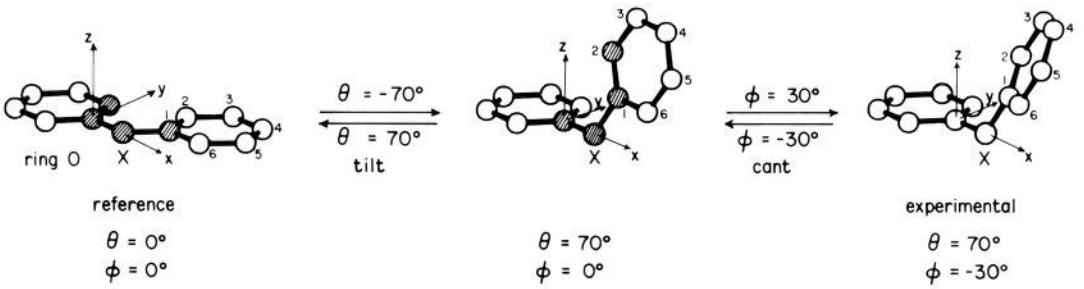

Figure 3. Definitions of the tilt angle θ and cant angle ϕ which specify the conformation of a substituted benzene molecule whose phenyl substituents are connected to the central ring (ring 0) by a single atom. The shaded atoms in the reference configuration are those whose torsional angle defines θ, and those in the middle figure define ϕ. The right-handed coordinate system is located on the carbon atom to which the substituent is bonded; the atom numbering scheme of the latter is indicated. In this illustration only one substituent is shown and the actual conformation is generated from the reference conformation by the operations $\theta = -70°$ and $\phi = 30°$.

generalized torsional angle A–B–C–D = C(1)–X–C(0)–C′(0) = C(2)–C(1)–X–C(0), the clockwise rotation of A to obtain superposition is positive. Consequently, counterclockwise rotations θ and ϕ are needed to pass from reference to actual configuration. The sign convention was chosen such that *a* and *b* substituents are associated with positive and negative values of θ, respectively. Note that θ and ϕ represent angles and rotational operations. Enantiomeric configurations have opposite signs of θ and ϕ.

Structure of $[Fe_4S_4(L{\cdot}S_3)Cl]^{2-}$. Cluster **8** was isolated as its Ph_4P^+ salt following the generation of **7** from ligand **5** and $[Fe_4S_4(SEt)_4]^{2-}$ and its reaction with pivaloyl chloride. These and related reactions are described below. The structure of the cluster compound was determined by single-crystal X-ray analysis. The crystal contains discrete cations and anions; the dimensions of the former are unexceptional[28] and are not considered further. A stereoview of the entire cluster structure and a depiction of the cluster unit itself are provided in Figure 4. Substituents are numbered as n = 1–6, as shown; atoms are labeled as (nx) where x is the atom number in leg n. Selected interatomic distances and angles are given in Table II. No symmetry is imposed on the cluster. It is immediately evident from Figure 4 that the desired structural result has been achieved.

The Fe_4S_4 unit is partially contained in a cavity whose floor is ring 0 and whose "sides" are the closest edge regions of rings 1, 3, and 5 of the corresponding arms. Points of attachment of the ligand to the cluster are atoms S(12,32,52). The cluster atom closest to the central ring, whose deviation from planarity is virtually nil, is S(4), which is positioned 3.74 Å above the ring centroid. The structure defines a *mono*-cluster anion of approximate trigonal symmetry in and around the cluster, whose differentiated site Fe(4) carries a terminal chloride ligand. Overall trigonal symmetry of the entire anion **8** is broken, somewhat unexpectedly, by the ligand, which does not exhibit alternating up-and-down substituents. Rather, it possesses the *aaabaa* conformation in which all substituents but leg 4 are above the plane of ring 0 in the direction of the cluster. The linking sulfur atoms of all substituents but leg 4 are depressed below the plane of this ring, with those of the arms further below the ring (0.34–0.45 Å).

Dispositions of individual substituents are specified partly by the ring 0/ring n dihedral angles in Table II and fully by the conformational angles in Table III. Coordination to the cluster causes the tilt angles of the three arms to be 35–40° larger than those of the two *a* legs. For arms 3 and 5, which are related by a pseudomirror plane normal to ring 0, the tilt angles differ by less than a degree while the cant angles depart by nearly 10°. For the "unique" arm 1, flanked by two *a* legs, the tilt is some 8° larger and the ring cant is opposite to that of the other coordinating legs. The rather small cant angles reveal that the phenyl rings of the arms are turned roughly edgewise toward the cluster. The angles S(n2)–Fe–S, involving Fe–S bonds external to the cluster core, divide into three sets, as listed in Table V, under idealized trigonal symmetry. These angles are notoriously deformable and irregular

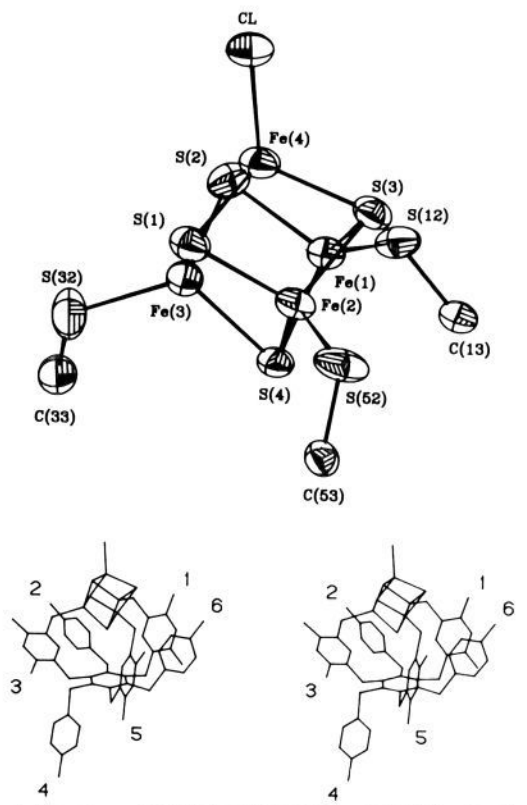

Figure 4. Structure of $[Fe_4S_4(L{\cdot}S_3)Cl]^{2-}$ (**8**) as its Ph_4P^+ salt. Upper: cluster portion with 50% probability ellipsoids and atom labeling scheme. Lower: stereoview of the entire structure and ring numbering scheme. Rings are numbered as n = 1–6 and S and C atoms as nx where x is an atom number of ring n.

in most $[Fe_4S_4(SR)_4]^{2-}$ clusters, often departing substantially from the tetrahedral value. In **8**, they reflect an approach to trigonal symmetry. The mean values of the angles (120 (1)°, 117 (3)°, 106 (2)°) seem to reflect a balance of cluster repulsion between the π-cloud of the central ring and the closest approach to preferred tetrahedral coordination at the Fe sites as permitted by the ligand in its observed conformation.

Cluster distances do not conform to the compressed tetragonal distortion from cubic stereochemistry of the $[Fe_4S_4]^{2+}$ core observed for most,[1,40] but not all,[41] $[Fe_4S_4L_4]^{2-}$ clusters with four

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(41) (a) Muller, A.; Schladerbeck, N.; Bögge, H. *Chimia* **1985**, *39*, 24. (b) Saak, W.; Pohl, S. *Z. Naturforsch.* **1985**, *40b*, 1105.

Table II. Selected Interatomic Distances (Å) and Angles (deg) for $[Fe_4S_4(L{\cdot}S_3)Cl]^{2-}$

Cluster			
Fe(4)–S(1)	2.281 (2)	Fe(4)–Fe(1)	2.757 (1)
Fe(4)–S(2)	2.304 (2)	Fe(4)–Fe(2)	2.778 (1)
Fe(4)–S(3)	2.297 (2)	Fe(4)–Fe(3)	2.780 (1)
Fe(1)–S(4)	2.283 (2)	Fe(1)–Fe(2)	2.742 (1)
Fe(2)–S(4)	2.281 (2)	Fe(1)–Fe(3)	2.776 (1)
Fe(3)–S(4)	2.291 (2)	Fe(2)–Fe(3)	2.763 (1)
Fe(1)–S(2)	2.286 (2)	mean	2.766 (15)
Fe(2)–S(3)	2.274 (2)		
Fe(3)–S(1)	2.290 (2)	S(4)–S(1)	3.600 (2)
Fe(1)–S(3)	2.291 (2)	S(4)–S(2)	3.577 (2)
Fe(2)–S(1)	2.284 (2)	S(4)–S(3)	3.602 (2)
Fe(3)–S(2)	2.284 (2)	S(1)–S(2)	3.595 (3)
mean	2.287 (8)	S(1)–S(3)	3.572 (3)
		S(2)–S(3)	3.627 (3)
Fe(1)–S(12)	2.257 (2)		
Fe(2)–S(52)	2.260 (2)	Fe(4)–Cl	2.226 (2)
Fe(3)–S(32)	2.267 (2)		
mean	2.261 (5)		

S(1)–Fe(4)–S(2)	103.26 (8)	Fe(1)–S(4)–Fe(2)	73.84 (6)
S(1)–Fe(4)–S(3)	102.55 (8)	Fe(1)–S(4)–Fe(3)	74.73 (6)
S(2)–Fe(4)–S(3)	104.07 (8)	Fe(2)–S(4)–Fe(3)	74.38 (6)
S(1)–Fe(3)–S(2)	103.64 (8)	Fe(1)–S(3)–Fe(2)	73.81 (6)
S(1)–Fe(3)–S(4)	103.63 (8)	Fe(1)–S(3)–Fe(4)	73.87 (7)
S(2)–Fe(3)–S(4)	102.87 (7)	Fe(2)–S(3)–Fe(4)	74.87 (7)
S(1)–Fe(2)–S(3)	103.18 (8)	Fe(1)–S(2)–Fe(3)	74.81 (7)
S(1)–Fe(2)–S(4)	104.12 (8)	Fe(1)–S(2)–Fe(4)	73.84 (7)
S(3)–Fe(2)–S(4)	104.50 (7)	Fe(3)–S(2)–Fe(4)	74.60 (7)
S(2)–Fe(1)–S(3)	104.85 (8)	Fe(2)–S(1)–Fe(3)	74.34 (6)
S(2)–Fe(1)–S(4)	103.05 (8)	Fe(2)–S(1)–Fe(4)	74.95 (7)
S(3)–Fe(1)–S(4)	103.91 (7)	Fe(3)–S(1)–Fe(4)	74.92 (7)
Cl–Fe(4)–S(1)	115.43 (8)	S(12)–Fe(1)–S(4)	120.81 (8)
Cl–Fe(4)–S(2)	113.99 (9)	S(52)–Fe(2)–S(4)	120.29 (8)
Cl–Fe(4)–S(3)	115.91 (8)	S(32)–Fe(3)–S(4)	119.83 (8)
S(12)–Fe(1)–S(2)	106.23 (8)	S(12)–Fe(1)–S(3)	116.22 (8)
S(52)–Fe(2)–S(3)	107.97 (8)	S(52)–Fe(2)–S(1)	115.04 (9)
S(32)–Fe(3)–S(1)	103.81 (9)	S(32)–Fe(3)–S(2)	120.7 (1)
Fe(1)–S(12)–C(13)	110.5 (2)		
Fe(2)–S(52)–C(53)	116.9 (2)		
Fe(3)–S(32)–C(33)	113.2 (2)		

Ligand			
S(12)–C(13)	1.778 (6)	S–C	
S(32)–C(33)	1.773 (7)	max	1.796 (6)
S(52)–C(53)	1.766 (6)	min	1.756 (6)
mean	1.772 (6)	mean of 12	1.776 (13)
C–C(phenyl)		C–C(methyl)	
max	1.413 (9)	max	1.524 (8)
min	1.371 (7)	min	1.510 (7)
mean of 42	1.388 (9)	mean of 9	1.516 (5)

C(11)–S(11)–C(10)	106.3 (3)	C(21)–S(21)–C(20)	105.8 (3)
C(31)–S(31)–C(30)	106.5 (3)	C(41)–S(41)–C(40)	103.2 (3)
C(51)–S(51)–C(50)	106.8 (3)	C(61)–S(61)–C(60)	105.2 (3)

Fe(1)S(12)C(13)/ring 1	107.0	ring 0/ring 1	72.5
Fe(2)S(52)C(53)/ring 5	22.6	ring 2	103.0
Fe(3)S(32)C(33)/ring 3	145.1	ring 3	110.3
		ring 4	101.3
		ring 5	104.8
		ring 6	77.3

Displacements[a] (Å) from Mean Plane of Ring 0

C(10)	+0.003	S(11)	−0.385
C(20)	+0.005	S(21)	−0.127
C(30)	−0.009	S(31)	−0.452
C(40)	+0.004	S(41)	+0.049
C(50)	+0.005	S(51)	−0.343
C(60)	−0.008	S(61)	−0.175

[a] Positive displacements are toward the cluster.

identical terminal ligands (L = RS^-, RO^-, halide). Nor is there a clear manifestation, in terms of individual Fe–S and Fe–Fe distances, of an *overall* trigonal distortion of the core. However,

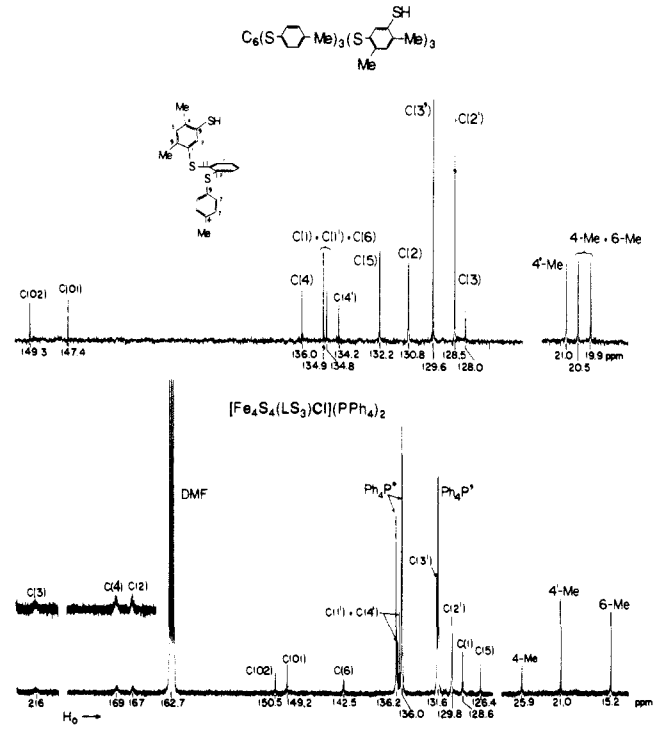

Figure 5. ^{13}C NMR spectra of ligand **5** (upper) in $CDCl_3$ and cluster **8** (lower) in DMF-d_7 solutions, consistent with the trigonal conformation *ababab* of both in solution. Signal assignments and the atom numbering scheme are indicated; the cation signal at 119 ppm is omitted.

the mean of the three Fe–S distances at differentiated subsite Fe(4) (2.294 (12) Å) is marginally longer than the mean values of the other three sets of Fe–S bond lengths related by trigonal symmetry (2.285 (5), 2.283 (8), 2.286 (4) Å). The trend is not reflected in Fe(4)–Fe separations. The Fe(4)–Cl bond length of 2.226 (2) Å agrees well with the mean value in $[Fe_4S_4Cl_4]^{2-}$[42] (2.216 (2) Å). Terminal Fe–S distances are normal. Consequently, the cluster unit may be described as metrically normal but lacking (idealized) trigonal or tetragonal symmetry. The irregular but small departures of core dimensions from a more nearly trigonal configuration may be mainly due to the nontrigonal ligand conformation, but disposition of this matter must await additional structure determinations. As will be seen next, the ligand conformation changes to a more symmetric arrangement upon passing to the solution phase.

The thiol/thiolate ligand substitution reactions[15a,43] offer a widely applicable method for introducing clusters into different ligand environments, such as those provided by various polythiols. In this way, Fe_4S_4 clusters have been wrapped with cysteinyl-containing peptides,[44] inserted in bovine serum albumin and insulin,[45] attached to functionalized silica gel[46] and organic polymers,[47] and captured by cyclic tetrathiols.[48] In all but one case, substitution of all Fe sites of the precursor cluster appears to be

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Table III. Conformational Analysis of Hexasubstituted Benzenes

compound	conformation		tilt and cant angles (deg) for arm or leg n						ref
			n = 1[a]	n = 2	n = 3	n = 4	n = 5	n = 6	
$C_6(OC_6H_5)_6$	*ababab*	θ =	78.65	−90.67	76.52	−72.92	101.11	−79.31	35
		ϕ =	23.77	20.05	6.81	−3.90	−32.80	12.02	
$C_6(SC_6H_5)_6 \cdot 2CCl_4$[b]	*ababab*	θ =	55.96	−55.96					20
		ϕ =	27.82	−27.82					
$C_6(OC_6H_3\text{-}3,5\text{-}Me_2)_6 \cdot MeCN$[c] no. 1[d]	*ababab*	θ =	75.10	−103.71	87.36				35
		ϕ =	26.67	12.69	2.64				
no. 2[d]	*ababab*	θ =	83.81	−107.01	99.50				
		ϕ =	37.64	14.74	−17.17				
$C_6(SC_6H_4\text{-}2\text{-}Me)_6$ (**6**)[c] no. 1	*bbaaab*	θ =	−61.69	−75.50	67.25	64.80	61.56	−72.75	*e*
		ϕ =	140.76	170.80	−140.53	−150.86	−149.70	132.04	
no. 2	*baabab*	θ =	−69.72	75.60	59.87	−44.56	131.71	−120.62	*e*
		ϕ =	170.91	−140.79	−142.4	−52.84	167.28	−137.25	
$C_6(SC_6H_4\text{-}4\text{-}Me)_3(SC_6H_2\text{-}3\text{-}SCH_2OMe\text{-}4,6\text{-}Me_2)_3$ (**4**)	*abbabb*	θ =	75.32	−70.48	−57.61	64.41	−52.29	−81.55	*e*
		ϕ =	9.96	−30.17	−40.21	40.19	−51.52	16.59	
$[Fe_4S_4(L\cdot S_3)Cl]^{2-}$ (**8**)	*aaabaa*	θ =	86.20	45.02	78.51	−75.37	77.76	52.52	*e*
		ϕ =	−12.49	53.98	0.04	−12.10	9.84	46.98	

[a] Carbon atom numbering scheme following the designation of crystallographic coordinates.[28] [b] Imposed S_6 symmetry. [c] Two crystallographically inequivalent molecules. [d] Imposed centrosymmetry. [e] This work.

complete. The exception is the species $[Fe_4S_4((Cys)_3\cdot peptide)(S\text{-}t\text{-}Bu)]^{2-}$, whose formulation is based on its NMR spectrum.[44a] This cluster has not been isolated and, because it does not contain a semirigid tridentate ligand, it is disadvantageous compared to the clusters prepared in this work for site-selective reactions.

Structures and reactions of $[Fe_4S_4(SR)_4]^{2-}$ clusters may be monitored by spectrophotometry and more incisively by NMR spectroscopy owing to isotropically shifted spectra that are extremely sensitive to structural differences. Although these species possess singlet ground states, paramagnetic levels of the spin manifold arising from antiferromagnetic coupling are populated at and near room temperature, accounting for isotropic contributions to the chemical shifts. Proton spectra of $[Fe_4S_4(SR)_4]^{2-}$ clusters have been illustrated and analyzed previously.[49] ^{13}C spectra of representative clusters have recently been reported.[50] Isotropic shifts of both nuclei arise dominantly or exclusively from contact interactions.

Clusters of significance in the experiments to be detailed in subsequent sections are the following:

$[Fe_4S_4(L\cdot S_3)(SEt)]^{2-}$ (**7**)

$[Fe_4S_4(L\cdot S_3)Cl]^{2-}$ (**8**)

$[Fe_4S_4(L\cdot S_3)(S\text{-}t\text{-}Bu)]^{2-}$ (**10**)

$[Fe_4S_4(L\cdot S_3)(S\text{-}p\text{-}C_6H_4Br)]^{2-}$ (**11**)

$[Fe_4S_4(L\cdot S_3)(SC_6H_3\text{-}2,6\text{-}Cl_2)]^{2-}$ (**12**)

$[Fe_4S_4(3\text{-}SC_6H_2\text{-}1\text{-}SCH_2OMe\text{-}4,6\text{-}Me_2)_4]^{2-}$ (**13**)

$[Fe_4S_4(SEt)_4]^{2-}$ (**14**)

$[Fe_4S_4(S\text{-}t\text{-}Bu)_4]^{2-}$ (**15**)

Solution Conformation. With neglect of small differences in tilt and cant angles of members of the sets of arms and legs, the *aaabaa* conformation of **8** in the crystalline state contains four inequivalent phenyl rings, and four inequivalent carbon atoms in ring 0 in the ratio 2:1:2:1. The complicated NMR spectra that would result from retention of this conformation in solution is not observed in DMF. Shown in Figure 5 are ^{13}C spectra of **8** and its ligand **5** together with proposed spectral assignments deduced from known chemical shift/structure correlations of benzene derivatives, spectral comparisons within the set of hexasubstituted

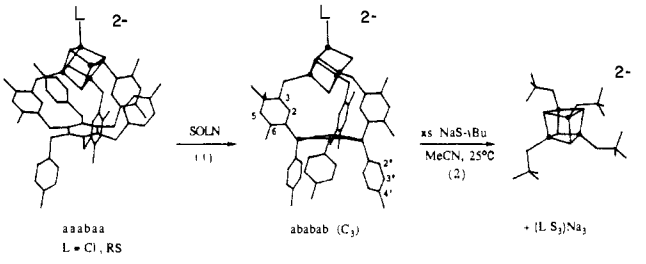

Figure 6. Depictions of (1) the conversion of cluster **8** to a trigonal conformation in solution and (2) the "all-or-nothing" reaction of **8** affording $[Fe_4S_4(S\text{-}t\text{-}Bu)_4]^{2-}$ (**15**) and ligand salt. The ligand numbering scheme applies to subsequent ^1H NMR spectra.

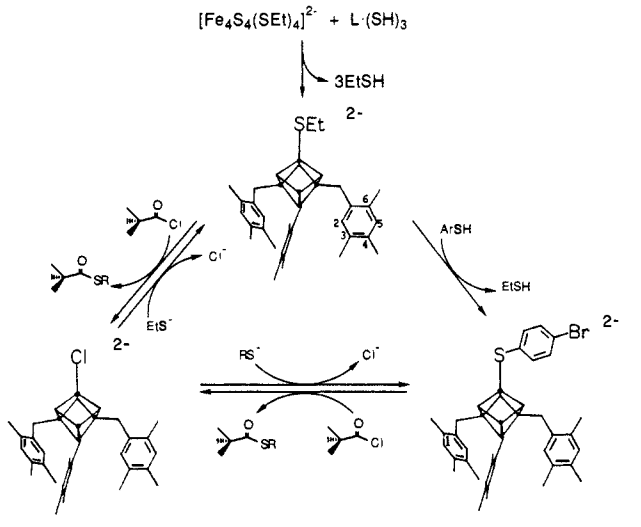

Figure 7. Summary of subsite-specific reactions of clusters containing a differentiated subsite.

benzenes prepared here, and shifts of $[Fe_4S_4(SR)_4]^{2-}$ clusters[50] (R = Ph and substituted phenyl). For each compound *two* resonances of ring 0 are observed, consistent only with conformations *aaaaaa* and *ababab*. Ring current contributions to chemical shifts of **5** cannot be explained on the basis of the first conformation.[51] We conclude that step 1 in Figure 6 has occurred, in which the two legs in the *a* position in the solid state adopt *b* positions in solution, i.e., on the side of ring 0 opposite the cluster.

Retention of the cubane-type core structure is independently demonstrated by the reversible 2−/3− redox step at $E_{1/2}$ = −1.03 V and an irreversible 3−/4− step at $E_{p,c}$ = −1.80 V for cluster **7**

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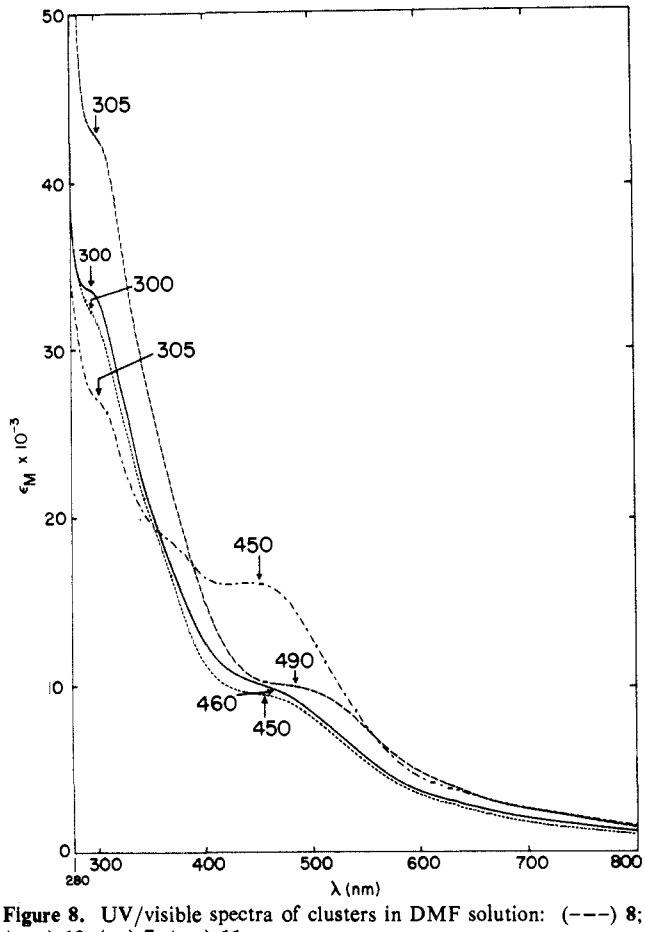

Figure 8. UV/visible spectra of clusters in DMF solution: (---) **8**; (- - -) **13**; (—) **7**; (- - -) **11**.

in DMF solution. Potential differences in the range of ca. 0.70–0.90 V are characteristic of $[Fe_4S_4L_4]^{2-}$ clusters (L = RS^-, halide).[52,53] As will be seen, ^1H NMR spectra of all clusters are also consistent only with trigonal conformational symmetry in solution.

Subsite-Specific Reactions. Ligand substitution reactions of types known to proceed to completion at all subsites of $[Fe_4S_4L_4]^{2-}$ clusters[1,15a,b,43,52] were investigated. These reactions have been followed by absorption spectra and ^1H NMR and are summarized in Figure 7, to which reference should be made in the subsequent discussion. All reactions were conducted in acetonitrile solution. With thiols as reactants, reactions were carried out under dynamic vacuum to remove volatile products and force reactions to completion. The residues were dissolved in CD_3CN, or in DMF for spectral examination. Sodium thiolates were added as Me_2SO solutions. When these or pivaloyl chloride were reactants, the reactions were examined in situ in CD_3CN solutions. Absorption spectra are presented in Figure 8. Cluster **13** (λ_{max} 450 nm) was isolated as its n-Bu_4N^+ salt from the ligand substitution reaction between **14** and thiol **3** (Figure 2). Because the ligands are substituted analogously to the arms in ligand **5**, the NMR spectrum of this cluster, shown in Figure 9, provides the basis for signal assignments in the clusters that follow. The 2-H and 4-Me signals are assigned as indicated from line width considerations; both are in ortho positions to the sulfur atom bonded to the paramagnetic core. All resonances fall in regions previously observed for a variety of arenethiolate clusters.[49] The resonance of 5-H, meta to the ligating sulfur atom, has proven particularly useful in following substitution reactions. The ligand numbering scheme for $[Fe_4S_4(L{\cdot}S_3)L']^{2-}$ clusters is given in Figure 6 and corresponds to that in Figure 9. Note that signals of the legs are denoted with primes.

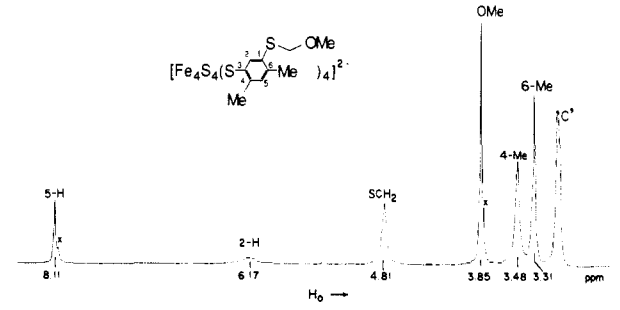

Figure 9. ^1H NMR spectrum of cluster **13** with terminal ligands having a substitution pattern analogous to that of phenyl rings in arms 1, 3, and 5 of cluster **8**. Signal assignments are indicated; C^+ = cation resonance.

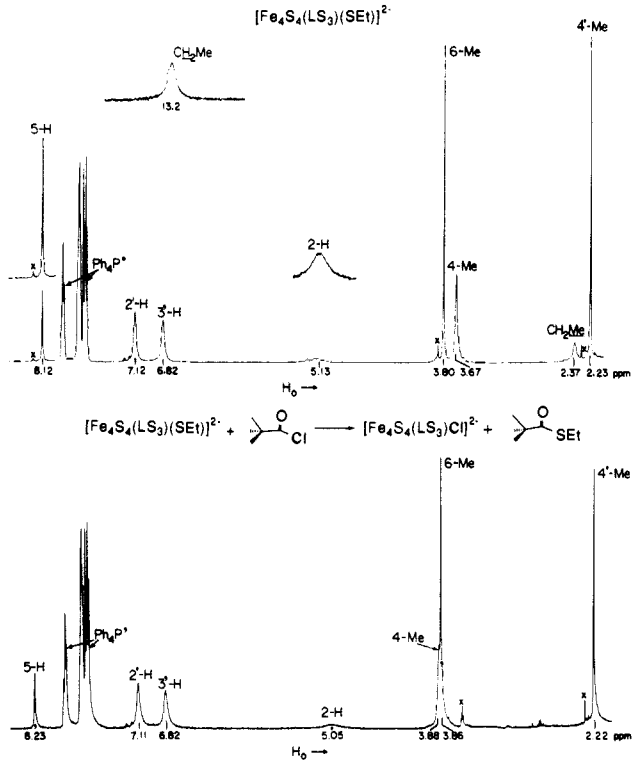

Figure 10. ^1H NMR spectra of CD_3CN solutions containing $[Fe_4S_4(L{\cdot}S_3)(SEt)]^{2-}$ (**7**) and its reaction product with 1 equiv of pivaloyl chloride. In these and subsequent spectra, signal assignments are indicated and x = impurity.

Cluster **7** (λ_{max} 300, 460 (sh) nm) was prepared from **14** and trithiol **5** in a ligand substitution reaction and is the precursor species for ligand substitution. Its spectrum, shown in Figure 10, features the 5-H resonance at 8.12 ppm and a broad methylene signal of the ethanethiolate ligand at 13.2 ppm, similar in position to that in the parent ethanethiolate cluster.[49a] Leg signals 2′-H and 3′-H were assigned by assuming that the former, being nearer the core, would experience the larger isotropic shift and temperature dependence of shift. Both isotropic shifts are much smaller than those of protons of coordinated thiolates (Figure 9). The signal due to 4′-Me was assigned on the same basis. These three resonances have practically constant shifts throughout the series of clusters.

Reaction of **7** with 1 equiv of pivaloyl chloride affords a product with no ethyl group signals (Figure 10), confirmed by isolation and structure determination to be cluster **8**, carrying a chloride ligand at the unique site. Its absorption spectrum is characterized by a pronounced red shift of the visible band to 490 nm. As in similar reactions,[52] the ethanethiolate ligand was removed as the thioester. Note the *single set* of signals in **7** and **8** and the response of arm signals to a change in ligand. In particular, the 5-H signal has been shifted downfield, to 8.23 ppm, in the chloride cluster.

Substitution of chloride in **8** has been examined by reaction with sodium 2-methyl-2-propanethiolate; NMR spectra are given

(52) Wong, G. B.; Bobrik, M. A.; Holm, R. H. *Inorg. Chem.* **1978**, *17*, 578.
(53) DePamphilis, B. V.; Averill, B. A.; Herskovitz, T.; Que, L., Jr.; Holm, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 4159.

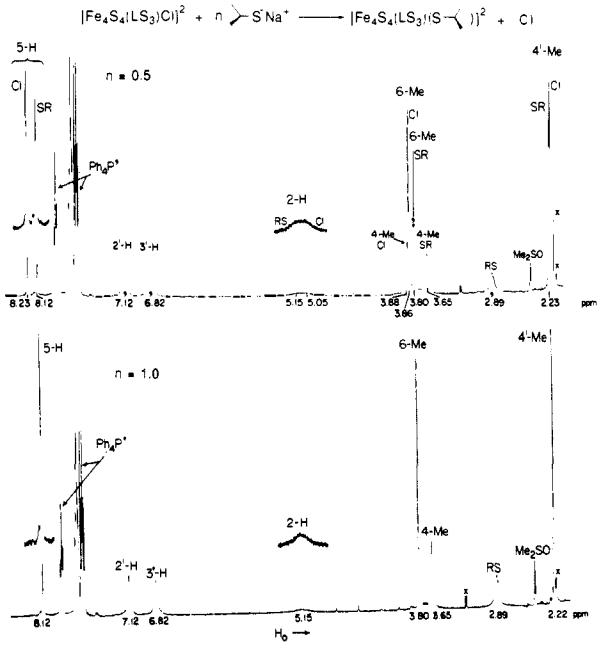

Figure 11. ^{1}H NMR spectra of the reaction products of $[Fe_4S_4(L{\cdot}S_3)Cl]^{2-}$ (**8**) with n = 0.5 (upper) and 1.0 equiv (lower) of NaS-*t*-Bu in CD_3CN solutions. RS and Cl designate resonances of $[Fe_4S_4(L{\cdot}S_3)(S\text{-}t\text{-}Bu)]^{2-}$ (**10**) and **8**, respectively.

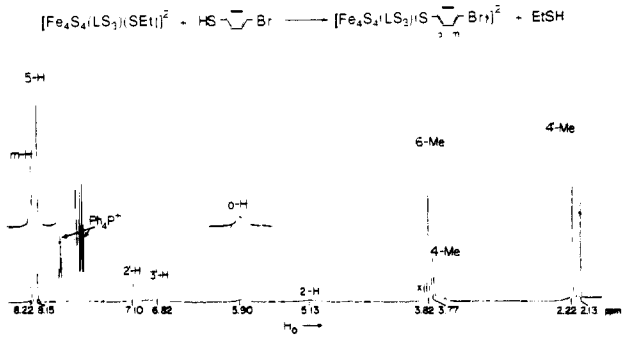

Figure 12. ^{1}H NMR spectrum of the reaction product of $[Fe_4S_4(L{\cdot}S_3)(SEt)]^{2-}$ (**7**) with 1 equiv of *p*-HSC_6H_4Br in CD_3CN solution.

in Figure 11. With 0.5 equiv of thiolate, only signals ascribable to **8** and **10** are present. The spectra clearly reveal the sensitivity of the 5-H shift to the ligand at the unique site. With 1.0 equiv of thiolate, the spectrum is that of **10** only. An analogous result has been obtained with 1.0 equiv of sodium ethanethiolate, affording **8**, and with sodium *p*-bromobenzenethiolate, which generates **11** (λ_{max} 300, 450 (sh) nm).

With 1 equiv of *p*-bromobenzenethiol, cluster **7** is converted quantitatively to **11** as shown in Figure 12. The *o*-H and *m*-H signals of the unique ligand are readily observed. This thiol was utilized to provide base line resolution of *m*-H and 5-H signals in the 8.1–8.2-ppm region. Other aromatic thiols react similarly, including 2,6-dichlorobenzenethiol which yields **12**. Treatment of either cluster with 1.0 equiv of pivaloyl chloride afforded **8**.

The foregoing results demonstrate that clusters containing one differentiated site undergo ligand substitution reactions that are immediate and are *specific* to that site. To the limits of NMR detection at 500 MHz, with 1.0–1.1 equiv of reactant, these reactions are *quantitative*. Given the greater lability of chloride than thiolate in $[Fe_4S_4(SR)_4]^{2-}$ clusters, specific displacement of chloride by thiolate is not unexpected. However, note that as active an electrophile as pivaloyl chloride distinguishes between the unique alkane- or arenethiolate and $L{\cdot}S_3$, even when the monofunctional ligand is somewhat sterically hindered, as in **12**. Reaction of the acyl chloride with the unique thiolate is rapid. However, when an additional equivalent of reagent was added, no reaction was observed for at least 15 min and the reaction was

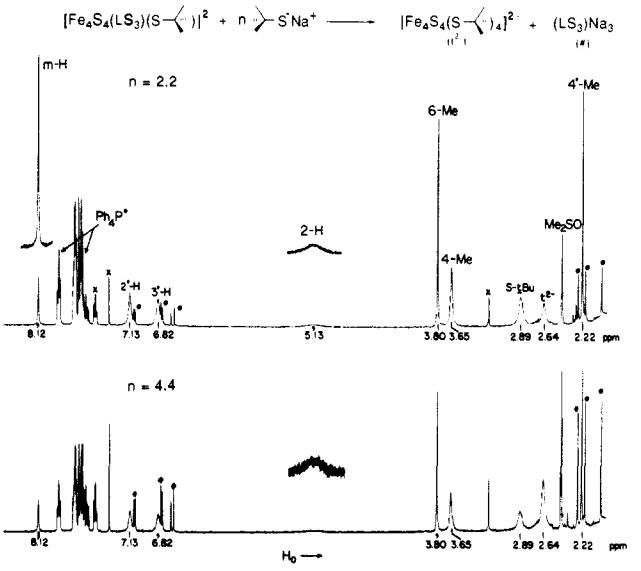

Figure 13. ^{1}H NMR spectra of reactants and products of $[Fe_4S_4(L{\cdot}S_3)(S\text{-}t\text{-}Bu)]^{2-}$ (**10**) with n = 2.2 (upper) and 4.4 equiv (lower) of NaS-*t*-Bu in Me_2SO solution. Signals of $[Fe_4S_4(S\text{-}t\text{-}Bu)_4]^{2-}$ (**15**) and the sodium salt of ligand **5** are designated by t^{2-} and #, respectively.

not complete after 3 h. This demonstrates the differential kinetic stability of the tridentate ligand to electrophilic attack. It is also noted that the absorption spectra of clusters derived from this ligand are unusual. Instead of well-defined visible maxima near 450 nm as found for $[Fe_4S_4(SPh)_4]^{2-}$, **13**, and related clusters,[53] the visible features are broad shoulders. Inasmuch as these bands have LMCT origin, this spectral difference is apparently related to the tilt and cant angles set by the ligand structure.

All-or-Nothing Reactions. In a further test of the stability of $[Fe_4S_4(L{\cdot}S_3)L]^{2-}$ clusters (L = Cl^-, RS^-), **10** in acetonitrile was treated with varying amounts of the strong nucleophile 2-methyl-2-propanethiolate as its sodium salt in Me_2SO. The results of two such experiments are shown in Figure 13. With 2.2 equiv of thiolate, the resultant NMR spectrum indicates the presence of unreacted **10**, new cluster **15**, and the trianion of ligand **5**. The two clusters are readily detected by their resolved *t*-Bu signals at 2.89 (**10**) and 2.64 (**15**) ppm. When 4.4 equiv were used, only these species were present in a much increased **15**:**10** ratio. These findings demonstrate that the $L{\cdot}S_3$ ligand system will yield to a competing alkylthiolate ligand either the Fe_4S_4 core in its entirety or nothing at all, i.e., an "all-or-nothing" stability.

Conformations of Hexasubstituted Benzenes. In addition to **4** and **5**, six other compounds of this type, but with identical substituents, were synthesized in good yield by the reaction of C_6F_6 or C_6Cl_6 with the sodium salt of the appropriate benzenethiol in DMEU solution. These compounds were prepared in order to examine further the solid and solution state conformations of hexasubstituted benzenes. The structures of triprotected ligand precursor **4** and $C_6(SC_6H_4\text{-}2\text{-}Me)_6$ (**6**) were determined by X-ray analysis. Stereoviews of the structures are provided in Figure 14.[28] Precise conformational descriptions are found in Table III.

Compound **6** exhibits two crystallographically independent molecules in space group $P\bar{1}$ with conformations *bbaaab* (#1) and *baabab* (#2). The angles C–S–C occur in the 101–108° range. Except for the orientation of substituent 4 in #2, methyl groups are turned outward away from ring 0. This tends to support the ligand design aspect of a 6-Me group in ligand **5** to cant the phenyl rings of the arms so that the thiol groups point inward. Other than $C_6(S\text{-}2\text{-naphthyl})_6$, this compound is the only one with six identical substituents that does *not* crystallize with the *bababa* conformation. Compound **4** as the acetone monosolvate also crystallizes in $P\bar{1}$. The structure is not as well determined as that of **6** because of substantial disorder of two of the methoxymethyl groups and the solvate molecule. However, the *abbabb* conformation was established, in which all three 6-Me groups of sub-

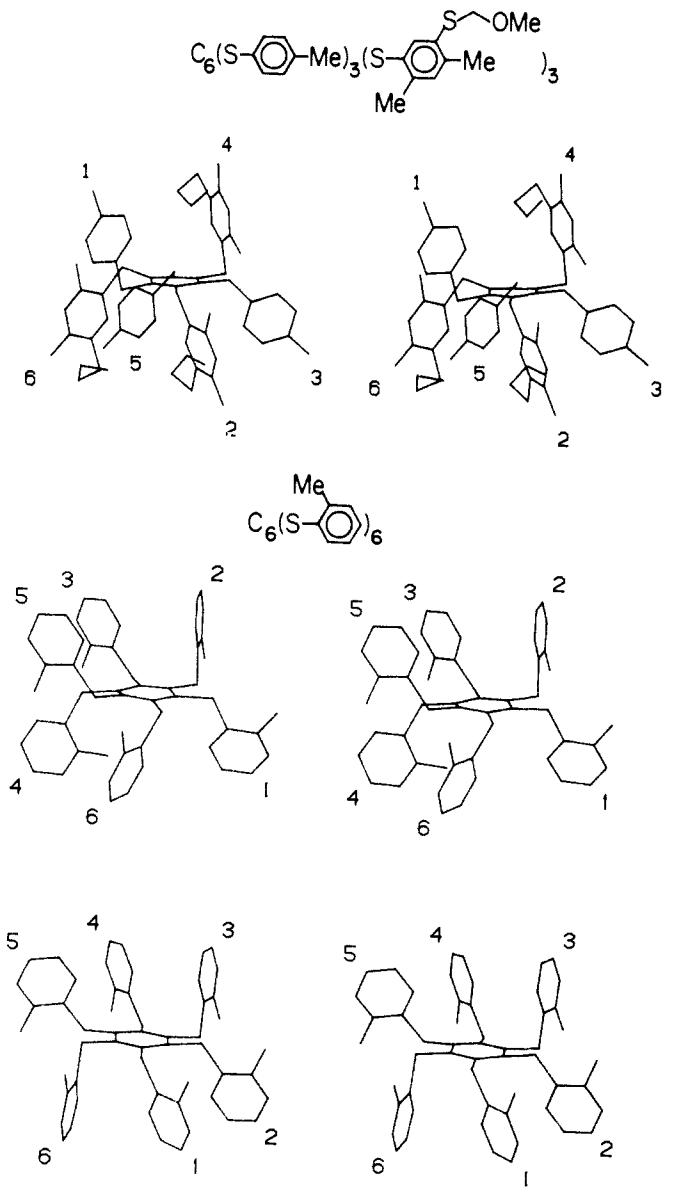

Figure 14. Stereoviews of the solid-state structures of the S-protected ligand **4** (*abbabb*) and two independent molecules of **6** (upper, *baabab*; lower, *bbaaab*) showing the indicated conformations.

stituents 1, 3, and 5 are oriented outward.

In solution, all hexasubstituted benzenes prepared in this work display ^1H and ^{13}C NMR spectra consistent in all aspects with the *bababa* conformation. Proton and ^{13}C spectra of **6** down to 210 K revealed no other conformers and gave no evidence of dynamic processes. Consequently, the less symmetric conformations of **4** and **6**, as that of cluster **8**, in the solid state must be largely set by crystal packing interactions. In the case of **6**, the trigonal conformation in solution could have the 2-Me groups oriented inward or outward relative to ring 0. The 6-H proton is located on the other carbon atom ortho to the C–S–C bonds connecting the substituents to ring 0. The ^1H NMR spectrum clearly shows the latter arrangement, or a fast exchange process favoring this arrangement. The 6-H doublet at 6.65 ppm is appreciably shielded by the ring 0 current effect relative to the other ring protons, which occur at 7.0–7.1 ppm. The spectrum of **4** reveals all ring protons at 6.8–6.9 ppm. Upon removal of the methoxymethyl protecting groups to afford trithiol **5**, the 2-H signal moves upfield from 6.83 to 6.45 ppm, again indicating a ring current effect on a proton located in an ortho position. Consequently, we conclude that the L·$(SH)_3$ ligand assumes a static or rapidly averaged trigonally symmetric conformation with an orientation of thiol groups particularly suited for binding to a single cubane-type core. This is a form of host–guest relationship that promotes favorable binding to cavitands;[31,32] i.e., *the ligand has the desired, predisposed conformation in solution for cluster binding.*

This research has demonstrated the feasibility of the synthesis of a semirigid trithiol ligand suitable for the binding of cubane-type cluster cores and the formation of Fe_4S_4 clusters with two differentiated subsites in a 3:1 ratio. Additionally, ligand substitution reactions with stoichiometric quantities of reagents are rapid, regiospecific at the unique site, and quantitative. With these clusters in hand, it should be possible to pursue by means of analogue systems the biological structure and reactivity matters noted at the outset. In this connection, it should be recognized that ligand **5** is well configured to accommodate a Fe_3S_4 core obtained by removal of a Fe atom from one vertex of the standard core of cluster **1**. This singly voided cubane arrangement is a likely structure of Fe_3S_4 clusters in proteins.[54-56] The ligand is designed so as not to incorporate the linear $Fe_3(\mu_2\text{-}S)_4$ core of $[Fe_3S_4(SR)_4]^{3-}$, the only Fe_3S_4 cluster type yet prepared outside a protein environment.[57] Other viable goals with the tridentate ligand and its site-functionalized clusters include the binding of heterometal MFe_3S_4 clusters, formation of bridged double-clusters similar to those in bacterial ferredoxins, and adjustment of core electron distribution and spin state by mono- and bidentate ligand variation at the unique site. Several of the studies are in progress and, together with the synthesis of other semirigid tridentates, will be the subjects of future reports.

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Registry No. 2, 107540-19-2; **3**, 113087-87-9; **4**, 113109-03-8; **5**, 107540-22-7; **5**·3Na, 113087-94-8; **6**, 113087-88-0; $(Ph_4P)_2$**7**, 113087-95-9; $\mathbf{7}^{3-}$, 113088-02-1; $\mathbf{7}^{4-}$, 113088-03-2; $(Ph_4P)_2$**8**, 113087-96-0; **10**, 113087-98-2; **11**, 113087-99-3; **12**, 107556-53-6; $(n\text{-}Bu_4N)_2$**13**, 113088-01-0; $(Ph_4P)_2$**14**, 113087-97-1; **15**, 51913-87-2; $C_6(SC_6H_4\text{-}4\text{-}OMe)_6$, 113087-89-1; $C_6(SC_6H_4\text{-}3\text{-}OMe)_6$, 113087-90-4; $C_6(SC_6H_4\text{-}4\text{-}OH)_6$, 113087-91-5; $C_6(SC_6H_4\text{-}4\text{-}SCH_2OMe)_6$, 113087-92-6; $C_6(SC_6H_4\text{-}4\text{-}SH)_6$, 113087-93-7; 1,3,5-trifluoro-2,4,6-tribromobenzene, 2368-49-2; *p*-tolylthiocuprate, 52403-06-2; 1,3-dimercapto-4,6-dimethylbenzene, 71056-12-7; chloromethyl methyl ether, 107-30-2.

Supplementary Material Available: Tables of X-ray crystallographic data for compounds **4**, **6**, and **8** and positional and thermal parameters, interatomic distances and angles, and calculated hydrogen atom positions (35 pages); listing of calculated and observed structure factors (127 pages). Ordering information is given on any current masthead page.

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