Molecular Recognition. Asymmetric Complexation of Diketopiperazines

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Synthetic receptors for neutral biochemical targets are of current interest in molecular recognition.[1] We describe here structures featuring convergent imide and lactam functions within cleft-like shapes; they show unusually high enantioselectivity ($\Delta\Delta G > 2.5$ kcal/mol) in their complexation of asymmetric diketopiperazines.

The structures were prepared (Scheme I) as described for Kemp's[2] triacid **2a**. Alkylation of hexahydrotrimesic esters followed by hydrogenation and then hydrolysis of **1b** afforded the new, highly soluble propyl[3] derivatives **2b** (>50% overall). Condensation with urea and activation ($SOCl_2$) gave the acid chloride **3**. Coupling to suitable diamines[4] led to the diimide diamides **4** and **5** (Scheme II). A two-step reduction procedure ($NaBH_4$, then acid) gave the polycyclic **6**; the meso isomer was separated by flash chromatography[5] from the racemate, and then further reduction (Et_3SiH/CF_3CO_2H) gave the lactams. The enantiomers (**7a** and **7b**) were resolved on a Pirkle column.[6]

Scheme I

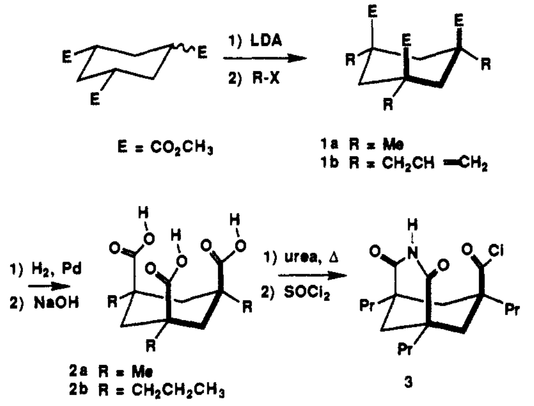


Table I. Binding of Diketopiperazines

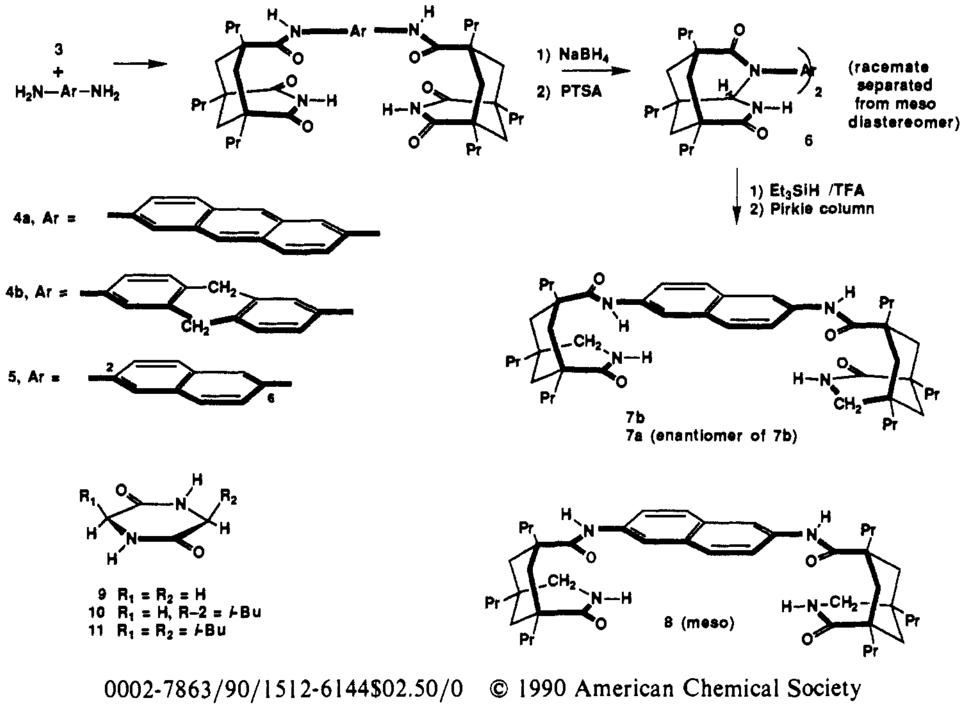
entry	host	equiv of **9** dissolved	titratn guest	K_a, M^{-1} (±10%) ($CDCl_3$, 296 K)
1	**4a**	<0.05	–	–
2	**4b**	0.4	–	–
3	**4b**	–	**10**	4800
4	**5**	0.7	–	–
5	**5**	–	**10**	50 000
6	**5**	–	**11**	12 000
7	**8** (meso)	0.45		
8	**8** (meso)	–	**10**	6700
9	**7a**	0.8	–	–
10	**7a**	–	**10**	2900
11	**7a**	–	**11**	840
12	**7b**	0.8	**10**	73 000
13	**7b**	–	**11**	82 000
14	**7b**	–	**10** (CD_3OD)	46

Two binding protocols were used: solid–liquid extraction of glycine anhydride **9** into $CDCl_3$ by sonication with the new structures, and homogeneous titrations[7] with the soluble *cyclo*-(L-leucylglycine) (**10**) and *cyclo*-(L-leucyl-L-leucine) (**11**) in the same solvent. The results are summarized in Table I.

Titrations with **10** and receptors **7** revealed a K_a of ~73 000 M^{-1} for one enantiomer, while the corresponding value for the other enantiomer was only 2900 M^{-1} (entries 10 vs 12). The 25-fold enantiomeric recognition corresponds to a difference of nearly 2 kcal/mol in relative binding affinities. The corresponding numbers for guest **11** (entries 11 vs 13) are nearly 100-fold ($\Delta\Delta G \approx 2.5$ kcal/mol). These are among the largest observed for chiral recognition of neutral substances.[8] The affinity is sufficiently high that binding is observed even in the competitive solvent MeOH-d_4 (entry 14).

A rationale for this difference is given in the proposed structure for the complex. With the appropriate match, e.g., **12**, four hydrogen bonds can be formed without unfavorable steric contacts elsewhere in the complex. The enhanced affinity of lactams vs imides observed here is in accord with recent theoretical[9] and

Scheme II



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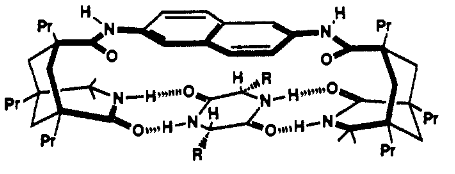
experimental[10] findings concerning the destabilizing effect of spectator atoms on nearby hydrogen-bonded arrays.



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[3] All new compounds were characterized by a full complement of high-resolution spectra; **2b** mp 210 °C dec; **3** mp 157–158 °C. **4a**, **4b**, **5**, and **8** mp >300 °C; **7** (racemic mp 174–176 °C, the enantiomers showed $[\alpha]_D = \pm 77.5°$ ($c = 1.1$, CH_2Cl_2).

[4] The diamines for **4a** and **4b** were obtained by Zn reduction of the corresponding anthraquinone. The 2,6-naphthalenediamine was obtained by Bucherer reaction of the diol: Chatt, J.; Wynne, P. *J. Chem. Soc.* **1943**, 33–36.

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[7] Titration data (NMR) were converted to association constants by nonlinear least-squares fit of the saturation plots; errors are estimated as ±10%.

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Synthesis, Structure, and Electrochemical Properties of Mixed-Ligand Iron–Sulfur Cubane Clusters with Two Cp* and Two Dithiolene Ligands (Cp* = η-C_5H_5, η-C_5Me_5)

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Cubane clusters containing an M_4E_4 core (M = transition metal, E = chalcogen) are known to have different types of structures, especially with respect to the M–M bonding of the cubane core.[1] A large number of homo- and heterometallic clusters of this type have been synthesized, but mixed-ligand, homometallic cubane clusters are rare.[1,2] Since the nature of cubane clusters greatly depends on the ligand environment of each metal in the cluster,[3] it is significant to synthesize new mixed-ligand, homometallic metal–chalcogen cubane clusters and to investigate their structures and properties. We now report the first synthesis, structure, and electrochemical properties of iron–sulfur cubane clusters with two Cp* and two dithiolene ligands.

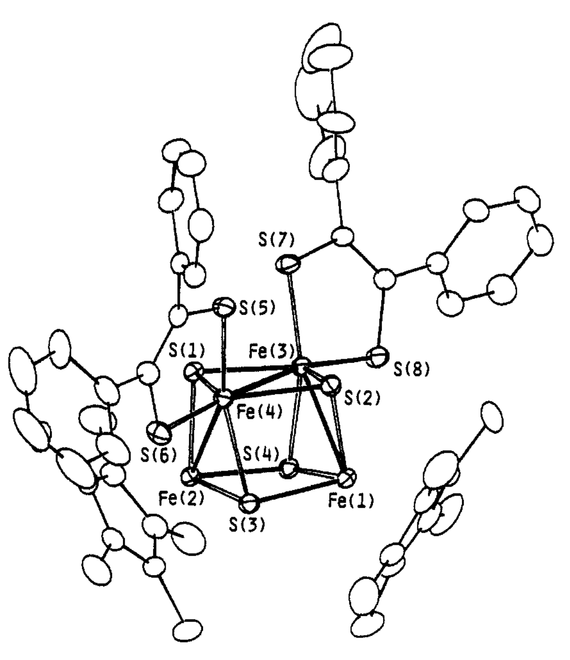
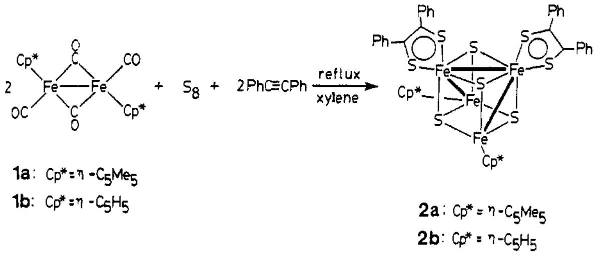


Figure 1. ORTEP diagram of $(\eta$-$C_5Me_5)_2(Ph_2C_2S_2)_2Fe_4S_4$ (**2a**) with thermal ellipsoids at the 30% probability level. Selected distances (Å): Fe(1)–Fe(3), 2.711 (1); Fe(2)–Fe(4), 2.717 (1); Fe(3)–Fe(4), 2.789 (1); Fe(1)···Fe(2), 3.400 (1); Fe(1)···Fe(4), 3.255 (1); Fe(2)···Fe(3), 3.270 (1) Å.

Reaction of a 1:0.5:2 molar ratio of $(\eta$-$C_5Me_5)_2Fe_2(CO)_4$ (**1a**), S_8, and PhC≡CPh in refluxing xylene for 120 h gave purple crystals of $(\eta$-$C_5Me_5)_2(Ph_2C_2S_2)_2Fe_4S_4$ (**2a**) as the major product in 51% yield. In a similar manner, the reaction of $(\eta$-$C_5H_5)_2Fe_2(CO)_4$ (**1b**) with S_8 and PhC≡CPh afforded $(\eta$-$C_5H_5)_2(Ph_2C_2S_2)_2Fe_4S_4$ (**2b**) in 32% yield (eq 1). In each case, a black powder, sparingly soluble in xylene, was also obtained as a byproduct, and in the latter case, the black powder was identified as the known cubane cluster $(\eta$-$C_5H_5)_4Fe_4S_4$ by mass and NMR spectroscopy.[4] This reaction is in sharp contrast to the reaction of $(\eta$-$C_5H_5)Co(CO)_2$ with S_8 and PhC≡CPh under similar conditions, which gives the mononuclear dithiolene complex $(\eta$-$C_5H_5)Co(S_2C_2Ph_2)$.[5]



(1)

Compounds **2a** and **2b** were characterized by the usual spectroscopic methods.[6] The FAB mass spectra of **2a** and **2b** show molecular ion peaks centered at m/z = 1106 and 966, respectively. The ^1H NMR spectrum of **2a** (200 MHz) in CDCl$_3$ exhibits a methyl singlet $(\eta$-$C_5Me_5)$ at 1.48 ppm and two Ph multiplets at 7.2–7.3 and 7.4–7.5 ppm. Similarly, the spectrum of **2b** shows

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[6] For **2a**: ^{13}C NMR ($CDCl_3$, 50 MHz) 10.6 (Me), 101.7 $(\eta$-$C_5Me_5)$, 127.2, 127.8, 129.8, 141.7 (Ph), 174.1 (S=CPh); MS (FAB, *m*-nitrobenzyl alcohol matrix, Xe) m/z 1106 (M^+). Anal. Calcd for $C_{48}H_{50}Fe_4S_8$-CH_2Cl_2: C, 49.38; H, 4.40. Found: C, 49.30; H, 4.49. For **2b**: ^{13}C NMR ($CDCl_3$, 50 MHz) 89.3 $(\eta$-$C_5H_5)$, 127.86, 127.92, 129.6, 141.6 (Ph), 179.0 (S=CPh); MS (FAB, *m*-nitrobenzyl alcohol matrix, Xe) m/z 966 (M^+). Anal. Calcd for $C_{38}H_{30}Fe_4S_8$-CH_2Cl_2: C, 44.55; H, 3.07. Found: C, 44.11; H, 3.36.

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