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Cooperative Dehydration of 1,1',2,2'-Ferrocenetetramethanol

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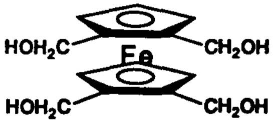
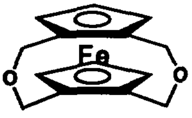
Summary: 1,1',2,2'-ferrocenetetramethanol (**1**) undergoes a remarkable acid-catalyzed tandem dehydration in aqueous solvents to give 1,1':2,2'-bis(oxybismethylene)ferrocene (**2**).

Cooperative phenomena are widely exploited by biological molecules for the purposes of binding and catalysis.[1] The essential features of cooperative binding have been incorporated into several synthetic hosts,[2-9] wherein an initial binding event induces conformational changes which lead to enhanced association constants for the subsequent binding events. In the course of our efforts to construct cooperative ferrocene-dicoronands, we have discovered that 1,1',2,2'-ferrocenetetramethanol (1) undergoes a remarkable acid-catalyzed tandem dehydration in aqueous solvents to give 1,1':2,2'-bis(oxybismethylene)-ferrocene (2) and not the homoannular isomer **3**. The stability of **2**--the simplest conceivable ferrocene-dicoronand--derives in part from a cooperative relationship between the two ether bridges.



1



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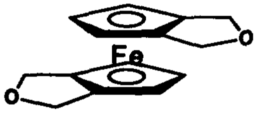
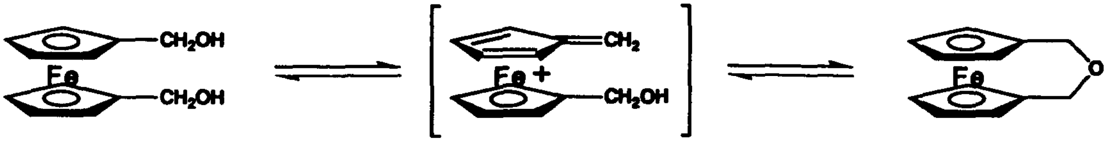


3

The first heteroannular cyclic ether of ferrocene was reported in 1960 by Rinehart and coworkers,[10] who dehydrated 1,1'-ferrocenedimethanol (4, Scheme I) with tosyl chloride in benzene to obtain 1,1'-(oxybismethylene)ferrocene (6). Several other groups[11-15] have also studied the dehydration of 1,1'-bis(1-hydroxyethyl)ferrocene to produce the corresponding α,α'-dimethyl-1,1'-(oxybismethylene)ferrocene. Yamakawa[16,17] has established that the latter dehydration proceeds stereospecifically *via* an S_N1 mechanism and that the extraordinary stability of the ferrocenylcarbinyl cation **5**[18] accounts for the facility and stereospecificity of this interconversion.

Scheme I

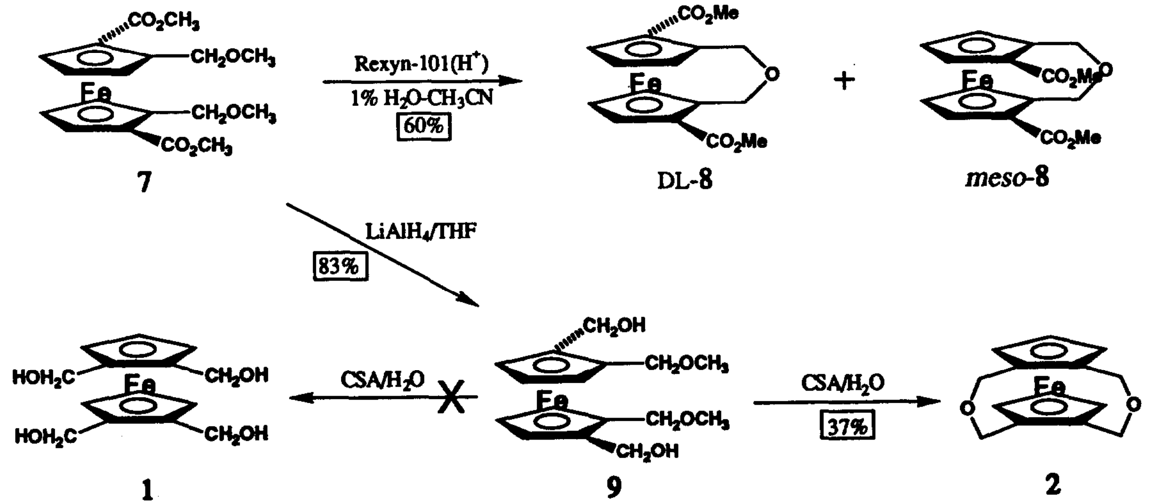


4 5 6

Compound **7**, produced by directed dilithiation of 1,1'-bis(methoxymethyl)ferrocene,[19] was reduced to diol-diether **9** (Scheme II), and conversion of **9** to tetramethanol **1** was attempted under conditions which readily afford **4** from **6** or from 1,1'-bis(methoxymethyl)ferrocene. However, a nonpolar, highly symmetric product was isolated.[20] The essential structural ambiguity was whether the two ether linkages are heteroannular (as shown for **2**) or homoannular as in structure **3**. Though the homoannular linkages might be expected to be less stable owing to angle strain, a five-membered, homoannular, cyclic ether of ferrocene has been reported,[21] and NMR does not provide any basis for distinguishing between the two possibilities. Our initial assignment of the product as **2** rested on our interpretation of the electron impact mass spectrum, which exhibits a molecular ion which is also the base peak. In our experience this behavior is typical of heteroannularly linked ferrocenes, whereas ferrocenes which lack such a tether readily fragment by separation of one of the Cp rings.

Definitive assignment of the structure emerged from single crystal x-ray analysis of the product (see Figure 1),[22] which is structurally (but, as it turns out, not crystallographically) analogous to the carbocyclic analogues reported earlier by Hillman et al.[23] Also in contrast to these carbocyclic analogs, the oxygens of **2** are not disordered in the crystal. The tilt angle between the Cp rings of **2** is about 16°,[22] which is greater than the 12° tilt found for **6**.[23]

Scheme II



It is in fact possible to isolate **1** by first hydrolyzing **7** (aqueous HBF_4) to give diol diester **10**, and then reducing to the tetramethanol ($LiAlH_4$, Scheme III). Tetramethanol **1** is extremely unstable in that exposure to miniscule amounts of acid (SiO_2, residual DCl in $CDCl_3$, glass surfaces) converts it to diether **2**. Indeed, even in solvents composed largely or entirely of water, **1** undergoes two dehydrations to afford **2** cleanly; we have been unable to hydrolyze **2** to **1**. This behavior contrasts sharply with that of dimethanol **4**, which is produced readily *via* hydrolysis of cyclic ether **6**. The mechanism of dehydration of **1** likely involves stepwise formation of the two ether linkages, with the stereochemical sense of the first ring closure being random, leading to the *meso* and DL intermediates **11** and **12**, respectively. Intermediates **11** and **12** can be prepared independently by reduction ($LiAlH_4$) of the separated diastereomers of **8** (Scheme II);[24] exposure of either **11** or **12** to aqueous acid leads to **2** quantitatively. Further dehydration of **12** requires opening of the ether linkage to give **1**, followed by initial closure to **11**. We believe that the ease of formation of **2** derives from preorganization of the two remaining alcohols in **11** so as to favor ether formation. This preorganization is manifested in the lack of free rotation of the Cp rings in **11** and in the tilting of the Cp rings toward each other.[23] Thus, the sequential dehydrations appear to be cooperative. A necessary correlate of this hypothesis is that $k_3/k_{-3} > k_2/k_{-2}$ (Scheme IV). We are currently performing experiments which will test this prediction.

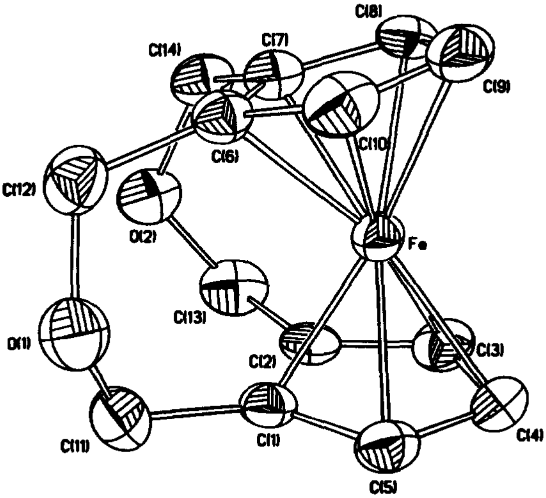
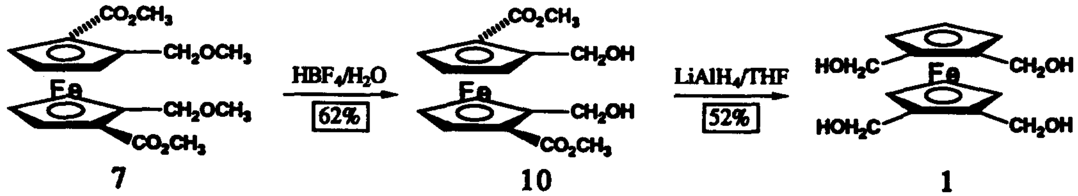
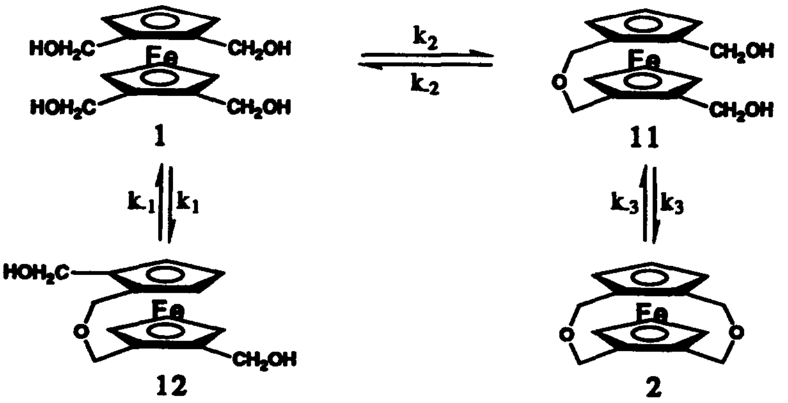


Figure 1. Structure of **2** as determined by single crystal x-ray analysis.[22]

Scheme III



Scheme IV



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20. Characterization of **2**: mp 92 °C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.21 (t, *J*=2.3 Hz, 2 H), 4.18 (d, *J*=2.3 Hz, 4 H), 4.02 (d, *J*=13 Hz, 4 H), 3.74 (d, *J*=13 Hz, 4 H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 84.0, 72.2, 71.1, 61.8 ppm; IR ($CHCl_3$) ν 3074, 2846, 1345, 1255, 1047, 1033, 801 cm^{-1}; MS (EI) *m/z* = 270 (M$^+$, 100), 213 (8), 179 (10), 134 (17), 91 (17), 56 (20) amu; HRMS *m/z* calcd for $C_{14}H_{14}O_2Fe$, 270.0343, *m/z* observed 270.0343.
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22. Compound **2** crystallizes in the $P2_1/n$ space group with the following parameters: R_F=4.99%, a=12.884(4) Å, b=12.012(4) Å, c=14.442(4) Å, β=101.45(3)°, V=2191(1) Å^3, *Z*=8 molecules/unit cell. The dihedral angle between the two Cp rings in **2** is 16.5° and 15.8° in the molecules which comprise the asymmetric unit.
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24. Previous work indicated that **7** is a single diastereomer,[19] so the observation that **8** is a mixture of diastereomers requires either an intriguing stereoisomerization or a reinterpretation of our earlier results. This will be clarified presently.

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