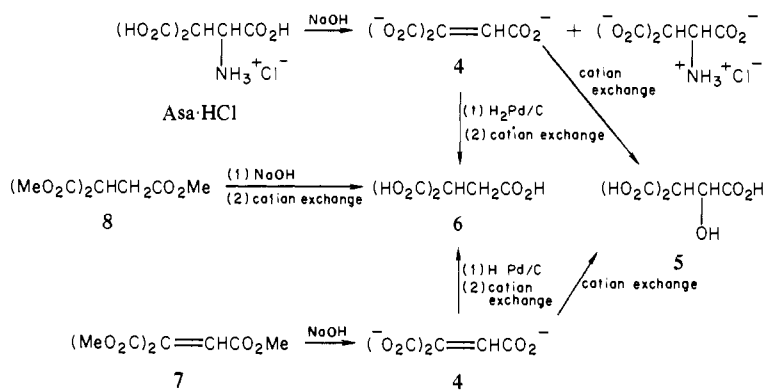


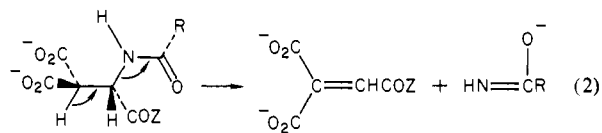
Scheme I



sample of Asa at 110 °C for 24 h in 2 M potassium hydroxide in a Teflon-lined, sealed vessel led to only 5% deamination as determined by ^1H NMR analysis.

The reactivity of Asa incorporated in a protein in basic medium was approximated by using dimethyl 5-hydantoinmalonate (**2**) as a model. The dimethyl ester is an acceptable model because ester saponification occurs prior to amide hydrolysis (vide supra). Heating **2** at 100 °C in a sealed, Teflon-lined vessel for 24 h in 2 M potassium hydroxide gave 55% Asa and 45% tricarboxyethylene as determined by ^1H NMR spectroscopy.

The extent of elimination as a function of pH can be explained in terms of the leaving group. Even with 3.5 equiv of sodium hydroxide at pH 10 some of the Asa is present with the amine functional group protonated, and the leaving group is ammonia. At higher pH Asa is completely deprotonated and elimination is much slower because the leaving group is amide. 5-Hydantoinmalonic acid is more reactive in 2 M potassium hydroxide with respect to elimination than is Asa because until the 1-2 amide bond of **1** is hydrolyzed, the leaving group is carboxamide. Carboxamide is resonance stabilized and leaves more rapidly than does amide. However, to achieve the geometry necessary for facile E2 or E1cB elimination mechanisms with resonance stabilization of the incipient carboxamide, initial hydrolysis of the 3-4 amide bond of the hydantoin is required. This hydrolysis allows for the necessary bond rotation to occur. The 3-4 amide bond of the hydantoin ring system is known to hydrolyze in basic medium before the 1-2 amide bond.¹⁰ In a protein or peptide containing Asa residues an initial amide hydrolysis is not required, and the elimination reaction should be at least as facile as in the model system. Hence, at least 45% of the Asa was probably lost during the hydrolysis of *E. coli* ribosomal proteins in 2 M potassium hydroxide¹ (see eq 2).



Henson and co-workers have also reported a synthesis of Asa.⁵ These authors imply that their final step, the saponification and hydrolysis of diethyl 5-hydantoinmalonate in 2 M potassium hydroxide at 100 °C for 24 h, was quantitative, even though the resulting Asa was never isolated. The results described above suggest that the yield of Asa from this step is actually less than 55% because of the facile elimination.

Quantitative measurement of peptide-bound Asa is unlikely from protein hydrolysis in basic medium. A more accurate measure of Asa may now require an initial chemical transformation of the malonic acid moiety prior to hydrolysis. Zytkevich and Nelsestuen have shown that the malonic acid moiety of peptide-bound Gla can be reduced to the tritiated 1,3-diol with tritiated diborane and the Gla detected as tritiated δ,δ' -dihydroxy-leucine by amino acid analysis after acidic hydrolysis.¹¹

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This methodology is presently under investigation for analysis of peptide-bound Asa.

Acknowledgment. We thank the National Cancer Institute (Grant CA-24665) and the General Medical Institute (Grant GM-24965) of the NIH for financial assistance. We also thank John Van Buskirk and Wolff Kirsch for stimulating discussions.

Registry No. 1, 80754-77-4; 2, 80754-78-5; 3, 5427-26-9; 4 trisodium salt, 80754-79-6; 5, 80754-80-9; 6, 922-84-9; 7, 51175-48-5; 8, 40967-67-7; β -carboxyaspartic acid, 75898-26-9; dimethyl sodiomalonate, 18424-76-5; 5-chlorohydantoin, 32282-43-2.

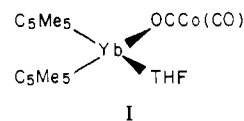
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Preparation and Crystal Structure of Bis[bis(pentamethylcyclopentadienyl)ytterbium(III)] Undecacarbonyltriferrate, $[(\text{C}_5\text{Me}_5)_2\text{Yb}]_2[\text{Fe}_3(\text{CO})_{11}]$: A Compound with Four Isocarbonyl (Fe-CO-Yb) Interactions

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It has been shown recently that the divalent lanthanide complex $(\text{C}_5\text{Me}_5)_2\text{Yb}(\text{OEt}_2)$ reduces $\text{Co}_2(\text{CO})_8$, cleaving the metal-metal bond to give I.^{1a} The tetracarbonylcobaltate anion is bonded to



the trivalent Lewis acid fragment $[\text{Yb}(\text{C}_5\text{Me}_5)_2(\text{THF})]^+$ by donation of a lone pair of electrons on one of the carbon monoxide groups. Infrared and X-ray data suggest that the carbon-oxygen bond of the bridging carbonyl ligand was significantly weakened, resulting in a charge disparity in the sense $\text{Co}(\delta^-)-\text{C}(\delta^+)-\text{O}(\delta^-)-\text{Yb}(\delta^+)$. This should enhance the reactivity of the bridging carbon monoxide group toward nucleophilic and/or electrophilic reagents. Such carbon- and oxygen-bonded carbonyl ligands have

*To whom correspondence should be addressed at the Chemistry Department, University of California, Berkeley, CA.

(1) (a) Tilley, T. D.; Andersen, R. A. *J. Chem. Soc., Chem. Commun.* **1981**, 985-986. (b) Infrared spectra have been used to suggest isocarbonyl interactions with f-block metal atoms: Marianelli, R. S.; Durney, M. T. *J. Organomet. Chem.* **1971**, *32*, C41-C43. Bennet, R. L.; Bruce, M. I.; Stone, F. G. A. *Ibid.* **1971**, *26*, 355-356. Crease, A. E.; Legzdins, P. *J. Chem. Soc., Dalton Trans.* **1973**, 1501-1507. Onaka, S.; Furuichi, J. *J. Organomet. Chem.* **1979**, *173*, 77-88. *Inorg. Chem.* **1980**, *19*, 2132-2136.

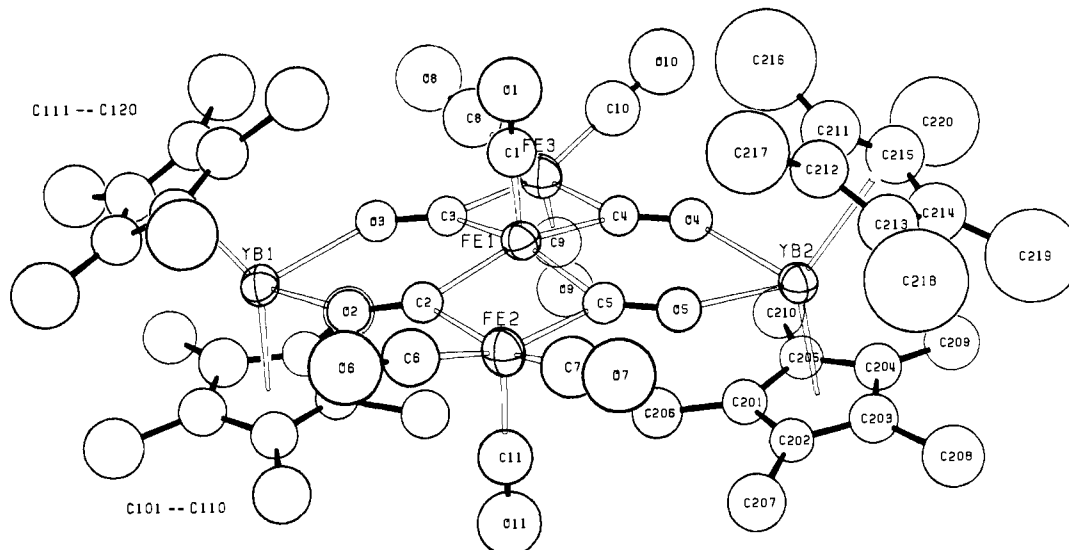


Figure 1. ORTEP drawing of $[(C_5Me_5)_2Yb]_2[Fe_3(CO)_7(\mu-CO)_4]$.

been shown to exhibit unique physical properties and reactivity patterns.²

In the investigation of the utility of $(C_5Me_5)_2Yb(OEt_2)$ in preparing complexes of transition-metal carbonyl anions that contain $M-CO-M'$ bonds, it was of interest to examine reactions of carbonyl clusters having bridging carbon monoxide groups. Carbonyl ligands that bridge two or more transition metals have a lower C-O bond order than terminal ones and are better σ donors toward hard Lewis acids. As a result, some Lewis acids induce terminal-to-bridge CO shifts.² Such interactions will result in further charge disparity in the bridging carbon monoxide group and activate the C-O bond to an even greater extent.

Reaction of 2 molar equiv of $(C_5Me_5)_2Yb(OEt_2)$ with $Fe_3(CO)_{12}$ in toluene or of stoichiometric amounts of $(C_5Me_5)_2Yb(OEt_2)$ and $Fe_2(CO)_9$ in toluene results in a dark red solution, from which violet prisms (mp 307–310 °C) of $[(C_5Me_5)_2Yb]_2[Fe_3(CO)_{11}]$ may be crystallized.³ The infrared spectrum shows that the carbonyl ligands are significantly perturbed relative to the electronically equivalent $[Et_4N]_2[Fe_3(CO)_9(\mu-CO)(\mu_3-CO)]$, which has $\nu(CO)(THF)$ at 1938 s, 1910 ms, 1890 sh, and 1670 $w\text{ cm}^{-1}$.⁴ The ytterbium complex shows two low-energy C-O stretching frequencies at 1667 and 1604 cm^{-1} , suggesting the presence of η^2, η^1 -triple bridging carbonyl ligands.

In order to unequivocally establish the structure of this novel complex, a crystal structure analysis was performed.⁵ Of the three discrete molecules in the unit cell, two are well-ordered and related by an inversion center while the third is disordered about the center of inversion. An ORTEP view of the ordered molecule is shown in Figure 1. The molecule has approximate C_{2v} symmetry about the Fe(1)–C(1) vector. The C_5Me_5 groups are inequivalent in the solid state as well as in solution since they give two equal-area resonances in the 1H NMR spectrum at 26 °C.³ The two iron–iron

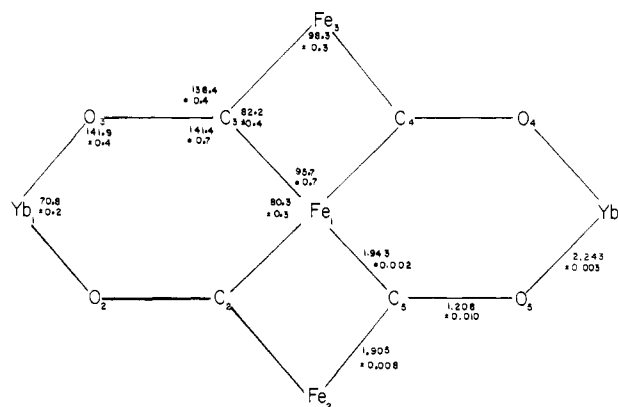


Figure 2. Line drawing showing some average bond lengths and distances. The average Fe(2,3)–C(terminal) and their associated C–O bond lengths are 1.741 ± 0.013 and 1.176 ± 0.014 Å, respectively. The Fe(1)–C(1) and C(1)–O(1) bond lengths are 1.698 (8) and 1.161 (9) Å, respectively. The average $Me_5C_5(\text{centroid})-Yb-Me_5C_5(\text{centroid})$ angle is $141.6 \pm 0.6^\circ$ and the $Me_5C_5(\text{centroid})-Yb$ bond length is 2.289 ± 0.019 Å.

distances [Fe(1)–Fe(2) and Fe(1)–Fe(3)] of 2.524 (1) and 2.538 (1) Å, respectively, are essentially equal, as are the four ytterbium–oxygen distances (average, 2.243 (5) Å). The average ytterbium–carbon(C_5Me_5) bond length of 2.573 (13) Å is similar to those found in ytterbium(III) metallocenes of the same coordination number [$Yb(C_5Me_5)_2S_2CNEt_2$, 2.63 (3)^{6a} and $Yb(C_5Me_5)_2(THF)Co(CO)_4$, 2.596 (1) Å¹]. However, this average bond length is significantly shorter than that found in the ytterbium(II) species of identical coordination number, $Yb(C_5Me_5)_2(py)_2$, 2.742 (7) Å.^{6b} This difference is expected since the ionic radius of Yb(III) is ca. 0.16 Å smaller than that of Yb(II) when both ions have the same coordination number.⁷ Thus, the paramagnetism of the complex is explained, since Yb(III) is an f^{13} ion whereas Yb(II) is an f^{14} ion and the complex can be viewed as a tight ion pair of the form $[Yb(C_5Me_5)_2]^+ [Fe_3(CO)_7(\mu-CO)_4]^{2-}$.

The Fe(2)–Fe(1)–Fe(3) angle is 161.8° , and there is no direct interaction between Fe(2) and Fe(3). The two planes defined by the carbonyls bound to Yb(1) and Yb(2) are inclined with respect to each other, with a dihedral angle of 168.1° away from the unique carbonyl bonded to Fe(1). Thus, the overall shape of the

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(3) Anal. Calcd for $C_{51}H_{71}Fe_3O_{11}Yb$: C, 44.6; H, 5.21. Found: C, 44.9; H, 4.63. IR (Nujol) $\nu(CO)$ 2048 w, 1998 s, 1973 s, 1667 w, 1604 bs cm^{-1} ; 1H NMR (PhMe- d_6 , 26 °C) δ 8.09 ($\nu_{1/2} = 130$ Hz), 6.11 ($\nu_{1/2} = 130$ Hz) due to the two inequivalent C_5Me_5 groups; μ_{eff} (solid state, 4–60 K): 3.91 μ_B per ytterbium; mp 307–310 °C.

(4) Lo, F. Y.-K.; Longoni, G.; Chini, P.; Lower, L. D.; Dahl, L. F. *J. Am. Chem. Soc.* **1980**, *102*, 7691–7701.

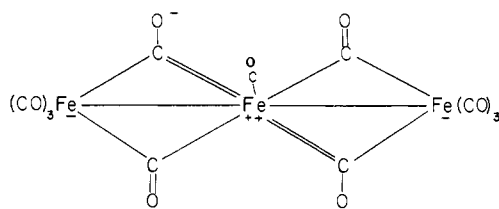
(5) The structure was solved by Dr. F. J. Hollander, staff crystallographer at the University of California at Berkeley X-ray crystallographic facility (CHEXRAY). Crystal data: $(C_5Me_5)_2Yb_2Fe_3(CO)_{11}$, $F_w = 1362.7$; space group, $P\bar{1}$, triclinic; $a = 14.525$ (2) Å, $b = 18.058$ (2) Å, $c = 18.324$ (2) Å; $\alpha = 72.151$ (11) $^\circ$, $\beta = 84.050$ (11) $^\circ$, $\gamma = 72.151$ (11) $^\circ$; $V = 4321$ (1) Å³; $\rho_{\text{calcd}} = 1.571$ g cm^{-3} ; $Z = 3$; $\mu(Mo K\alpha) = 40.05$ cm^{-1} ; $\lambda = 0.71073$ Å. The structure was solved by Patterson and Fourier methods and refined with 8622 data [$F^2 > 3\sigma(F^2)$] measured on a Nonius CAD 4 diffractometer. The R and R_w for all data were 5.76% and 8.33%, respectively.

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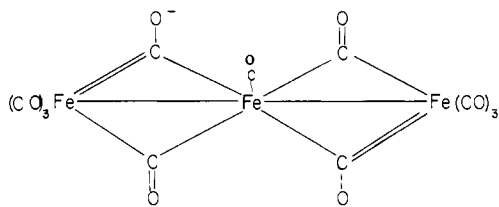
(7) Shannon, R. D. *Acta Cryst.* **1976**, *32A*, 751–767.

cluster might be described as an inverted umbrella, the handle being the unique carbonyl bound to Fe(1). The least-squares plane defined by the bridging carbonyl carbon atoms C(2), C(3), C(4), and C(5) is 0.36 Å below Fe(1) and above Yb(1) and Yb(2) by 0.56 and 0.48 Å, respectively. The terminal Fe(2) and Fe(3) atoms are slightly below this plane, by 0.06 and 0.02 Å, respectively.

The bonding iron-iron distances are similar to those found in the electronically equivalent (48 electron) triiron clusters $[\text{Fe}_3(\text{CO})_9(\mu\text{-CO})(\mu_3\text{-CO})]^{2-}$,⁴ $[\text{Fe}_3(\text{CO})_{10}(\mu\text{-H})(\mu\text{-CO})]^{-}$,^{8a} and $\text{Fe}_3(\text{CO})_{10}(\mu\text{-CO})_2$.^{8b} The latter three clusters have their iron atoms at the corners of an isosceles triangle, the geometry usually found for trimetallic cluster molecules.⁹ The geometry of the $[\text{Fe}_3(\text{CO})_7(\mu\text{-CO})_4]^{2-}$ cluster (Figure 2 shows the averaged bond angles and lengths within the cluster) has been greatly perturbed by the presence of the two $[\text{Yb}(\text{C}_5\text{Me}_5)_2]^+$ units, which have forced four carbonyl groups into bridging positions. The Fe(1)CO(4)-CO(5) and Fe(1)CO(2)CO(3) fragments may be viewed as metallaacetylacetonate groups coordinated in a chelating fashion to the two ytterbium(III) centers.¹⁰ Thus, the $\text{Fe}_3(\text{CO})_{11}^{2-}$ cluster may be viewed, in an electronic sense, by the valence bond structures shown below (IIa and IIb), in which each of the terminal



IIa



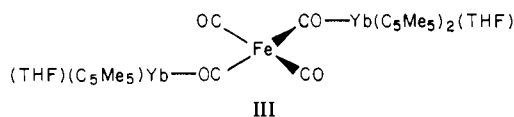
IIb

iron atoms have 18 valence electrons and the central iron atom has 16 valence electrons. These valence bond structures are only approximations to the true electronic structure, and a molecular orbital treatment will be much better. However, the valence bond representations emphasize the formal analogy to that of a metallaacetylacetonate ligand. In order to act as a chelating ligand, the $[\text{Fe}_3(\text{CO})_{11}]^{2-}$ distorts by breaking an Fe-Fe bond. This process does not require much energy since the Fe-Fe bond energy in $\text{Fe}_3(\text{CO})_{12}$ is estimated to be ca. 19 kcal mol⁻¹,¹¹ most certainly less than that of four ytterbium-oxygen bonds.

A rich reaction chemistry is suggested by the "opened" geometry of the $[\text{Fe}_3(\text{CO})_{11}]^{2-}$ cluster. However, toluene solutions of the $[(\text{C}_5\text{Me}_5)_2\text{Yb}]_2[\text{Fe}_3(\text{CO})_{11}]$ cluster did not react with H₂ or CO at 18 atm during a 24-period.

In order to examine reactions of the complete set of binary iron carbonyls with the ytterbium(II) metallocene, we have studied the reaction of Fe(CO)₅ with 2 molar equiv of Yb(C₅Me₅)₂(OEt₂). The reaction gives $[\text{Yb}(\text{C}_5\text{Me}_5)_2(\text{thf})]_2[\text{Fe}(\text{CO})_4]$ after crystallization from tetrahydrofuran.¹² The complex gives Fe(CO)₄(SnPh₃)₂ upon reaction with Ph₃SnCl, as shown by infrared spectroscopy.¹³ Thus, the complex may be formulated as the

tetracarbonylferrate, III, analogous to the well-known sodium salt, Na₂Fe(CO)₄.¹⁴



III

Acknowledgment. This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy under contract Number W-7406-ENG-48. We also thank the NSF for a grant to the Chemistry Department used to purchase the X-ray diffractometer. We thank a referee for helpful comments.

Registry No. $[(\text{Me}_5\text{C}_5)_2\text{Yb}]_2[\text{Fe}_3(\text{CO})_7(\mu\text{-CO})_4]$, 80878-91-7; $[(\text{Me}_5\text{C}_5)_2\text{Yb}(\text{thf})]_2[\text{Fe}(\text{CO})_4]$, 80890-27-3; Fe₂(CO)₉, 15321-51-4; Fe₃(CO)₁₂, 17685-52-8; Fe(CO)₅, 13463-40-6; (Me₅C₅)₂Yb(OEt₂), 74282-47-6.

Supplementary Material Available: A listing of thermal and positional parameters (6 pages). Ordering information is given on any current masthead page.

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Stereospecific Synthesis of the C30-C43 Segment of Palytoxin by Macrocyclically Controlled Remote Asymmetric Induction

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We recently reported that the conformational structure of macrocyclic compounds provides a unique, well-defined medium through which widely separated asymmetric centers may interact effectively.¹ This conclusion follows from the observation that simple monosubstituted macrolactones and macrocycloalkanones undergo a variety of highly stereoselective addition reactions that appear to be controlled by the conformation(s) of the macrocycle involved. Mechanistic points aside, the major value of that work lies in its implications to the synthesis of complex arrays of stereocenters on conformationally flexible molecular frameworks. In this communication, we describe our first application of the approach as a central strategy for the control of acyclic stereochemistry. Thus the lipophilic segment (1, R, R' = H) of the complex marine toxin palytoxin² (1, R = C₂₉H₅₁O₁₆N₂, R' = C₈₁H₁₄₂O₃₆N) was prepared stereospecifically from propylene oxide via the medium ring lactone 2 (see Figure 1).

Selection of an appropriate macrocyclic intermediate for the effective control of stereochemistry is crucial to the success of our approach to remote asymmetric induction. The requirements for such an intermediate would be simply that it be prepared easily and that it react via a conformation that will yield the desired relative stereochemistry at newly formed asymmetric centers. As described below, the evaluation of potential systems in the context of these requirements may be assisted by molecular mechanics calculations.³ These simple calculations are quite revealing with respect to conformations and strain energies and suggest here that

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