

an interconversion of AI intermediates presumably through a zwitterionic species.³ Our results also support this conclusion since we do not see any trans-fused intermediates and only one of the four possible cis-fused AI intermediates. It is possible that a trans-fused AI intermediate never forms and that an initially formed zwitterionic intermediate collapses down to the cis-fused AI. It is unlikely, however, that the collapse of the zwitterion would produce only one of the possible AIs, and it is more probable that equilibration among the possible AI intermediates is occurring to produce the isomer with the least steric strain, 1. This equilibration may also explain the broadening in the resonances of 1.

Registry No. 1, 126156-51-2; 1 (conjugate acid), 126652-65-1; 11, 126156-52-3; *N*-methyl-1,2,4-triazoline-3,5-dione, 13274-43-6; *trans*-cycloheptene, 45509-99-7.

Radiometallacarboranes as Tumor Imaging Reagents

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Received March 19, 1990

Monoclonal antibodies (Mab), when conjugated with bifunctional chelation reagents containing a radiometal, have provided sensitive and accurate imaging agents for the detection of cancer and other diseases.¹ The bifunctional chelates presently in use are generally of the aminocarboxylate family and subject to catabolism with release of metal ion *in vivo*. We have now designed, synthesized, and evaluated a functionalized cluster containing a radiotransition metal (venus flytrap cluster, VFC) which makes use of an inorganic ligand set, incorporates exceedingly strong cluster bonding based upon a bridged *commo*-bis(dicarbollide) structure,² and can be prepared in the aqueous media³ commonly used to supply radiometal salts. The species reported here presages the existence of a large family of functionalized metallacarborane clusters which may serve as biologically inviolable radio-transition-metal carriers for the antibody-mediated γ -imaging or β -therapy of tumors.

Scheme I presents the synthesis of the diastereomeric VFC precursors and their conversion to the corresponding isomers of the very stable Co^{3+} -VFC-COOH (*dl*- and *meso*-4). The synthesis of the diastereomers of 2 from *closo*-1,8- $\text{C}_2\text{B}_9\text{H}_{11}$ ⁴ and the anion of 4-carbomethoxypyrazole was suggested by the well-known nucleophilic opening of this carborane by reaction with electron-pair donors to produce *nido*-10-substituted-7,9- $\text{C}_2\text{B}_9\text{H}_{11}$ species⁴ having a weakly acidic bridge hydrogen atom between BH vertices 10 and 11. Conversion of 2 to the formal 7,9-bis-(dicarbollide) intermediates, 3, and thence to 4 involves the loss of both of the B-H-B bridge protons present in 2 and hydrolysis of the carbomethoxyl function in the presence of Co^{3+} and aqueous

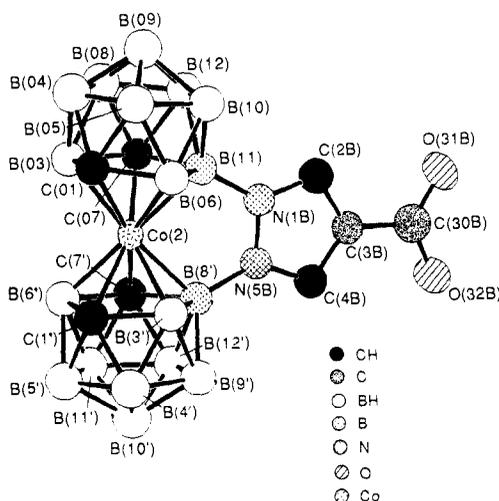
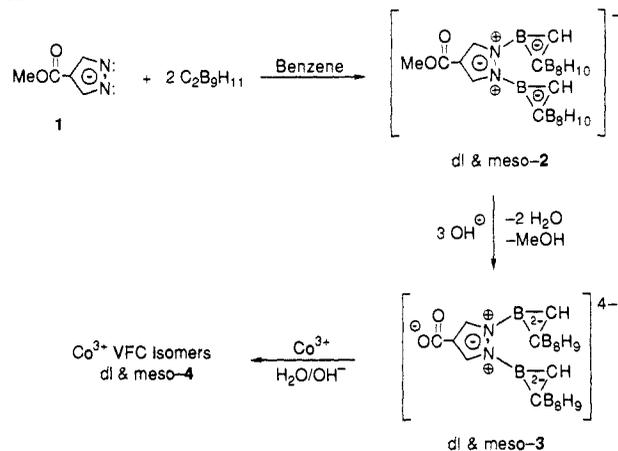


Figure 1. ORTEP representation of *meso*-4 with hydrogen atoms removed for clarity, showing the numbering scheme. Interatomic distances from Co, in Å: C(01), 2.085 (9); C(07), 2.061 (8); C(11), 2.077 (9); C(7'), 2.056 (9); B(03), 2.088 (11); B(06), 2.079 (11); B(11), 2.034 (10); B(3'), 2.103 (11); B(6'), 2.072 (11); B(8'), 2.039 (10).

Scheme I



KOH at pH 13 (15 min at 100 °C). Acidification and extraction with diethyl ether affords a mixture of *dl*- and *meso*-4 in up to 50% combined yields. The scope of this reaction sequence has been investigated by using precursors derived from unsubstituted pyrazole anion combined with Ni^{3+} and Cu^{3+} as well as Co^{3+} present in the VFC products. The structures of the chromatographically separated *meso*- Cu^{3+} , *meso*- Ni^{3+} , and *dl*- Co^{3+} have been determined crystallographically and the structures of the Co^{3+} isomers correlated with their ¹H and ¹¹B FT NMR spectra. These results will be reported elsewhere.

The structure of *meso*-4 has been determined crystallographically (Figure 1), and the results have been used to correlate the ¹H and ¹¹B FT NMR spectra and HPLC retention times of the *meso* and *dl* isomers. Both isomers of 4 exhibit the characteristic stability of the *commo*-7,8- and -7,9-bis(dicarbollide) complexes of Co^{3+} .

Conversion of the mixture of isomeric 4 species to their active *N*-hydroxysulfosuccinimide esters was carried out by using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide in acetonitrile, and the diastereomeric product mixture, 5, was purified by reverse-phase HPLC using a C_8 column (62% yield). High conjugation yields were achieved with 5 and model lysine-containing peptides. Reaction of 5 which contained radioactive ⁵⁷Co ($t_{1/2}$ = 271 days, γ -emission) with the anticarcinogenic antigen Mab T84.66⁵ produced a conjugate which carried, on the average,

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0.05 $^{57}\text{Co}^{3+}$ VFC per Mab molecule after purification by HPLC. The conjugated Mab retained >90% of its original immunoreactivity by enzyme immunoassay. The tumor targeting properties of the antibody conjugate were evaluated in nude mice with human colon tumor xenografts over a period of 168 h. Excellent γ -imaging was attained, and biodistribution studies showed a steady increase of both tumor/liver (T/L) and tumor/blood (T/B) ratios with time (T/L and T/B were, respectively, 2.88 and 1.21 after 48 h, and 3.48 and 1.40 after 168 h). The results of imaging and biodistribution experiments will be presented in detail elsewhere, but they suggest that the VFC concept has great potential for tumor imaging and therapy.

Acknowledgment. We thank the National Institutes of Health for support of this research under Grants RO1-CA31753 and PO1-CA43904.

Supplementary Material Available: Tables of bond distances and angles, positional and equivalent isotropic thermal parameters, and anisotropic thermal parameters, details of the crystallographic data collection for *meso-4*, experimental data on the preparation of 2 and 4 and conjugation of $^{57}\text{Co-4}$ to T84.66 Mab, collection and reduction of X-ray data, and solution and refinement of the structure of *meso-4* (13 pages); tables of observed and calculated structure factors (16 pages). Ordering information is given on any current masthead page.

Cooperative Behavior in the Redox Activity of the 12-Heteropolytungstates

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Received February 20, 1990

The 12-heteropolyacids (12-HPAs) of interest as solid and homogeneous solution catalysts can function as Brønsted acids and multielectron oxidants and are used extensively for production of short-chain alkenes and methacrylic acid from a variety of compounds.¹⁻⁸ Recently, Misono⁵⁻⁸ and co-workers have observed that the aldehyde yield can be improved by employing a series of mixed-metal 12-HPAs, the $\text{H}_3\text{PMo}_{12-x}\text{W}_x\text{O}_{40}$ solid solutions, where $x = 0-12$. One of their results⁷ (Figure 1a) reflects an approximately parabolic dependence of the excess yield of glutaraldehydes on the metal content (Mo and W) in the catalyst. The excess yield is the difference between the actual and expected yields, the latter weighted by mole fraction using the yield associated with the end points $x = 0, 12$. The functional form of this curve is very similar to the excess energy curves found for solid solutions.⁹ In this communication, we provide an explanation of Figure 1a via a theoretical scheme with close links to the solid-solution problem.^{9,10}

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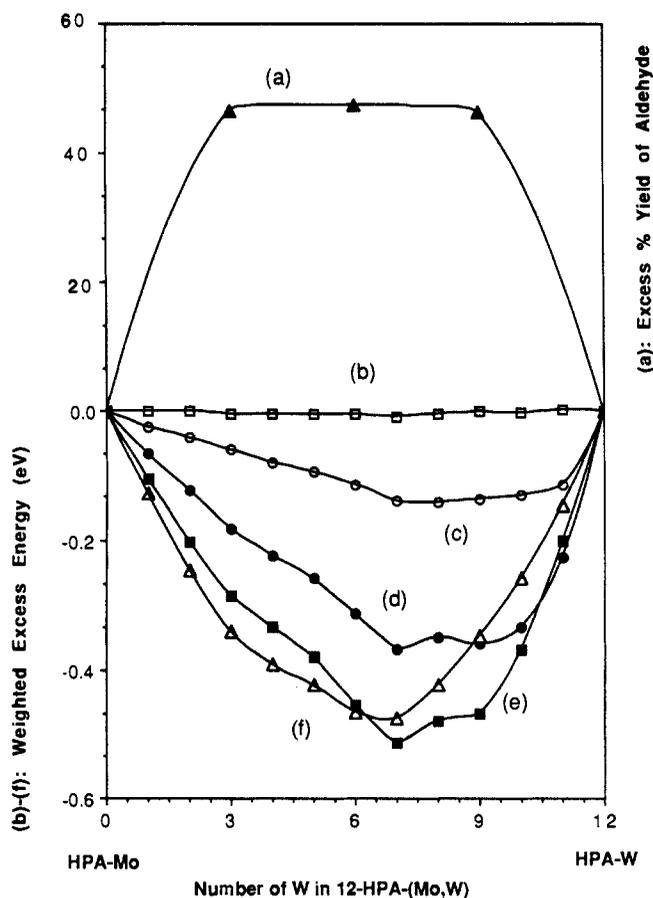


Figure 1. (a) Excess percentage yield of glutaraldehyde (Misono's result). (b-f) Computed excess energy of the 12-HPA-(Mo,W) cluster solution after the cluster has captured (b) 0, (c) 1, (d) 3, (e) 5, and (f) 12 electrons.

The heteropolyanions are of the widely known Keggin type,³ which consists of $\text{PM}_{12}\text{O}_{40}^{n-}$ units ($M = \text{Mo}, \text{W}, \text{or V}$) weakly linked together. Since the redox activity of the 12-HPA-(Mo,W) solid solution takes place in the primary structure, we consider the structure of a single Keggin cluster rather than the infinite solid. We examine the entire set of $\text{PMo}_{12-x}\text{W}_x\text{O}_{40}^{3-}$ cluster solutions ($x = 0-12$) relying on earlier spectroscopic and structural studies^{4b,11} which suggested the existence of either isomeric anions of a single composition fixed by x or solid solutions containing anions of different Mo:W ratios centered around x .¹⁰

Using the EHMO method, we have evaluated the energies of all possible structures for the polyanionic clusters, $\text{PMo}_{12-x}\text{W}_x\text{O}_{40}^{3-}$ (where $x = 0-12$). Since previous structural studies^{11,12} have indicated that the cluster dimensions are independent of their Mo/W content, we kept the structure fixed for the series. The $\text{PMo}_{12-x}\text{W}_x\text{O}_{40}^{3-}$ composition has 12 possible arrangements for $x = 1$ or 11 and 66 for $x = 2$ or 10. For $x = 3-9$, there is a large set of permutations. Since the Keggin cluster has a slightly distorted tetrahedral symmetry, use of an idealized structure considerably reduces the number of permutations.

If the ion $\text{PMo}_{12-x}\text{W}_x\text{O}_{40}^{3-}$ is denoted as $[\text{Mo}_{12-x}\text{W}_x]$, the excess energy of a permutation of a selected $[\text{Mo}_{12-x}\text{W}_x]$ solution is defined as

$$\Delta H_{\text{excess}}[\text{Mo}_{12-x}\text{W}_x] = H_{\text{ch}}[\text{Mo}_{12-x}\text{W}_x] - H_{\text{ideal}}[\text{Mo}_{12-x}\text{W}_x] \quad (1)$$

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