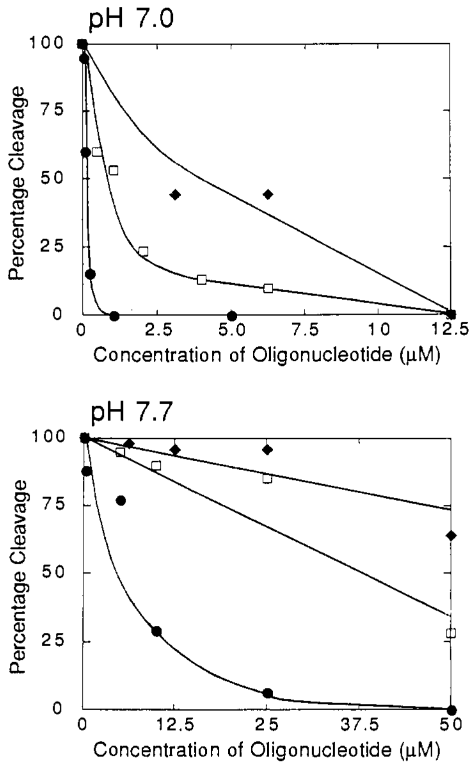

Figure 2. Specific inhibition of *Ksp*632 I cleavage by intermolecular triplex formation: plots of percentage cleavage of the DNA fragment versus the concentration of oligonucleotide in the reaction mixture at pH 7.0 and pH 7.7. The symbols on the plot indicate the oligonucleotides with 5-methylcytosine and an acridine (**3**) (●), 5-methylcytosine only (**2**) (□), and the natural 17-mer (**1**) (◆). Assays were performed by using a *Not*I–*Hin*dIII restriction fragment of pDCI,[13] labeled at one end by ^{32}P, which contains a single *Ksp*632 I cleavage site within the 17-bp recognition site for triple-helix formation. The triple helix was formed in restriction buffer A (33 mM Tris acetate, 33 mM potassium acetate, 0.5 dithiothreitol, 10 mM $MgCl_2$, and 100 μM spermine, at pH 7.0 or 7.7) by incubation for >1 h at 30 °C in order to avoid kinetic effects. Three units of *Ksp*632 I (Boehringer Mannheim) was then added and the mixture incubated for a further 20 min before the reaction was stopped with the addition of EDTA to 50 mM. Cleavage was analyzed by PAGE and quantified by using an LKB laser densitometer, using exposures within the linear range of the film.

5′ end of the oligonucleotide via a pentamethylene linker (Figure 1, panel B). Methylation of cytosines increases the affinity of the third strand for the duplex,[2,10] as a result of a small p*K* change and the formation of a helical spine of hydrophobic methyl groups in the major groove, and an acridine covalently attached to the 5′ end of the oligomer is able to intercalate site-specifically into the DNA at the triplex–duplex junction (Figure 1, panel A), increasing the affinity of the third strand for the target duplex.[11]

We tested the effect of these modifications on inhibition of protein binding to DNA by determining the relative concentrations required for 50% inhibition of cleavage of DNA by the restriction endonuclease *Ksp*632 I. The results of these experiments are shown in Figure 2 and summarized in Table I. Both of these modifications can substantially reduce the concentration required to inhibit cleavage (Figure 2). At both pH 7.0 and pH 7.7, substitution of 5-methylcytosine for cytosine produces an approximately 5-fold increase in inhibition of cleavage, and the presence in addition of an acridine residue covalently attached to the 5′ end of the oligomer produces an overall 30-fold increase in inhibition of cleavage over the unmodified oligomer (Table I). These results reflect the increase in the melting temperature of the triplex-to-duplex transition (Table I) resulting from these modifications. The increased concentrations of all oligodeoxynucleotides required for inhibition of *Ksp*632 I cleavage at pH 7.7 compared to pH 7.0 reflect the inherent dependence of intermolecular triplex formation on protonation of cytosines. The oligoacridine was able to give 100% inhibition of *Ksp*632 I cleavage at only 1 μM at neutral pH. This is the first demonstration of *complete inhibition* of endonuclease cleavage *at neutral pH* by intermolecular triplex formation.

We have shown that modification of oligonucleotides can be effectively used to strongly increase the competitive inhibition of protein binding to DNA via intermolecular triplex formation. This will allow the design of effective inhibitors of gene transcription or DNA replication and, thus, the production of potential therapeutic agents or tools for investigating the biological function of specific segments of DNA in a highly selective manner.

Acknowledgment. This work was supported in part by a European Molecular Biology Organization Long Term Fellowship (ALTF 119-1989) to D.A.C.

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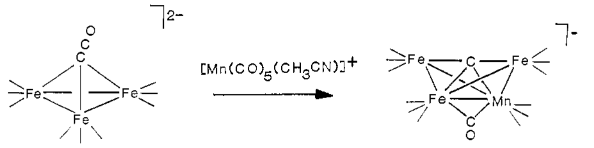
Synthesis and Crystal Structure of a Four-Metal Ketenylidene: $[PPN]_2[Fe_3CuI(CO)_9(CCO)]$

Anuradha S. Gunale, Michael P. Jensen, Charlotte L. Stern, and Duward F. Shriver*

Department of Chemistry, Northwestern University
Evanston, Illinois 60208-3113

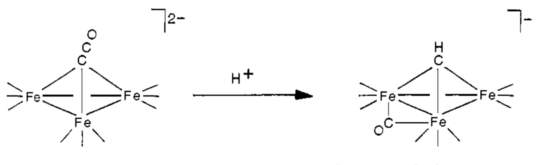
Received October 5, 1990

The reactions of the coordinated ketenylidene ligand, CCO, have received considerable attention in part because of its interesting and varied chemistry.[1-4] This chemistry includes both metal cluster building reactions and a variety of transformations of the CCO ligand. The majority of ketenylidene complexes are trimetallic carbonyl clusters and cluster building reactions on these lead to carbide clusters resulting from the cleavage of the C–CO bond, eq 1.



(1)

The addition of H^+ to $[PPN]_2[Fe_3(CO)_9(CCO)]$ (I) also results in the cleavage of the α-C–β-CO bond and formation of the methylidyne, eq 2.[2] By contrast, protonation of the ruthenium analogue, $[PPN]_2[Ru_3(\mu\text{-}CO)_3(CO)_6(CCO)]$, occurs on the metal framework with retention of the ketenylidene ligand.[3b]



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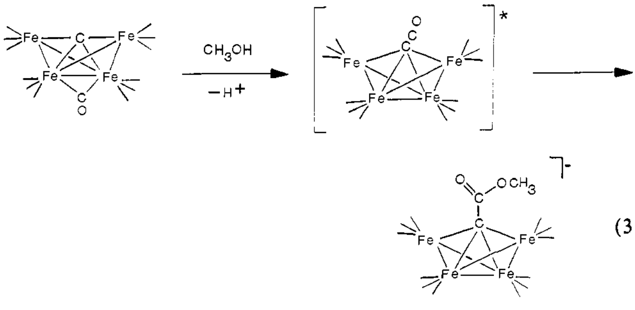
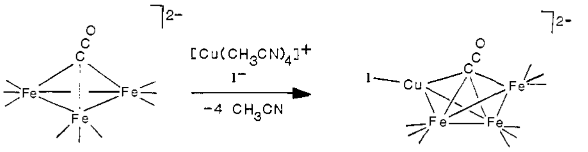
In pioneering research on iron carbide clusters, Bradley and co-workers postulated that a transient four-metal ketenylidene might exist as shown in eq 3.[5] This intermediate was not observed; rather, it was proposed by analogy to the reactivity of several trimetal clusters. In this communication, we report the first synthesis and unambiguous characterization of a heterometal butterfly cluster containing a μ_4-CCO ligand.



(3)

The rapid reaction of $[Cu(CH_3CN)_4][PF_6]$[6] (50 mg) and I (200 mg) in acetonitrile (4.0 mL) under dry nitrogen, followed by addition of [PPN]I (87 mg),[7] produced the new ketenylidene cluster, $[PPN]_2[Fe_3CuI(CO)_9(CCO)]$ (II), eq 4.



(4)

The solvent was removed under vacuum and the remaining oils were extracted into dichloromethane (4.0 mL). The addition of diethyl ether (7.0 mL) caused the PPN salt of cluster II to precipitate as an oily solid, which was collected by filtration. $[PPN][PF_6]$ remaining in the filtrate was discarded. Recrystallization from dichloromethane/diethyl ether (or pentane) provided II as dark brown crystalline solid in 42–83% yield. A subsequent X-ray structure determination revealed that the crystal contains one molecule of CH_2Cl_2 per formula unit of cluster.[8]

The infrared spectrum of II in CH_2Cl_2 shows CO stretches at 2024 (m), 1952 (s), and 1877 (m) cm^{-1}. These are shifted to higher frequencies than in I, 1924 (s) and 1872 (m) cm^{-1},[2] consistent with the addition of a Lewis acidic fragment to the cluster. The ^{13}C NMR spectrum of II, prepared from I enriched with ^{13}C at all cluster carbon atoms,[2] in CD_2Cl_2 at room temperature shows a strong, sharp carbonyl peak at 218.8 ppm, and resonances for the β- and α-carbons at 180.4 and 68.9 ppm, respectively, $J(CC) = 74$ Hz. The latter are shifted from the resonances shown by I: 222.3, 182.2, and 90.1 ppm, $J(CC) = 74$ Hz.[2] The positions and C–C coupling demonstrate that the ketenylidene structure is retained in solution.

A single-crystal X-ray structure determination of II reveals a four-metal butterfly with copper on one wingtip, Figure 1.[9] This contrasts with the structure of related four-metal carbides where the heterometal has been found exclusively in a hinge position, as shown in eq 1.[4]

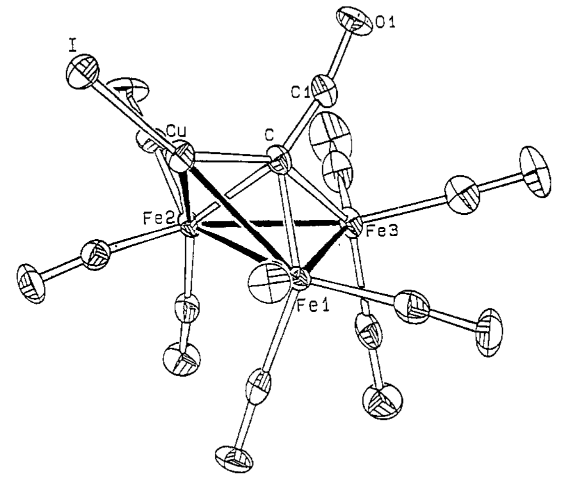


Figure 1. ORTEP drawing of the cluster dianion in $[PPN]_2[Fe_3CuI(CO)_9(CCO)]$ (II). The atoms are represented by 35% probability thermal ellipsoids. Relevant bond distances: $C–C_1$, 1.317 (8); $C_1–O_1$, 1.180 (7); $Fe_1–C$, 1.955 (5); $Fe_2–C$, 1.971 (5); $Fe_3–C$, 2.046 (5); Cu–C, 2.008 (5) Å.

The α-carbon of the ketenylidene in II is bonded to all four metal atoms. The original iron ketenylidene triangular metal framework is unchanged within experimental error. The $C–C_1$ and $C_1–O_1$ distances of the CCO ligand, 1.317 (8) and 1.180 (7) Å respectively, are close to those of the parent I: 1.28 (3) and 1.18 (3) Å. The ketenylidene ligand is significantly bent in II (∠CCO 167.0°) which compares with 172.8° for I.[2]

In the case of M_4 carbide clusters, such as $[RhFe_3(CO)_{12}C]^{-}$[4] and $[Fe_4(CO)_{12}C]^{2-}$,[10] the hinge M–M distance is typically shorter than the four hinge–wingtip M–M bonds, and the M (wingtip) array is nearly linear.[4] The d_π and d_σ interactions between the wingtip iron atoms with the carbide atom account for this short and nearly linear Fe–C–Fe array.[11] By contrast, the butterfly ketenylidene II contains a longer Fe–Fe hinge distance, 2.605 (1) Å, than the average hinge–wingtip distance, 2.558 (1) Å, and the Cu(wingtip)–C–Fe(wingtip) array is longer and decidedly bent (152.4°). Apparently the ketenylidene ligand remains intact in II because the carbon and copper atoms cannot participate in strong M(wingtip)–C–M(wingtip) π and σ interactions. This lack of strong Cu–C d_π and d_σ interaction can be attributed to the existence of a filled d shell at low energy for the Cu(I) center. For similar reasons, copper and the other group 11 metals do not form carbide phases whereas iron and other group 8 metals do.[12]

The structural changes just noted for butterfly carbide clusters are also seen for nitrido clusters,[13] which are isostructural with the carbides. The two crystallographically independent molecules of $[H_3Ru_4(CO)_{11}N]$ have nearly linear wingtip–nitride–wingtip angles of 174.0 (2)° and 173.4 (2)° and hydride-bridged hinge bond lengths of 2.811 (1) and 2.810 (1) Å, respectively.[14] The corresponding isocyanato cluster, $[H_3Ru_4(CO)_{12}NCO]$,[15] demonstrates the effects of functionalizing the nitride atom are even more dramatic than for the carbide of II. The wingtip–nitrogen–wingtip angle decreases to 106.1 (2)°, and the wingtip–nitrogen bond lengths increase from 1.972 (4) [1.962 (4) Å] and 1.953 (4) Å [1.954 (4) Å] in the nitride cluster to 2.144 (4) and 2.151 (4) Å in the isocyanate complex. The hinge bond also lengthens to 2.949 (1) Å. The isocyanate structure is similar to halide-bridged butterflies,[15–17] while the less exaggerated features of the ketenylidene cluster II are more typical of those observed when η^2 ligands are coordinated to butterfly frameworks.[18]

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(9) Crystal data for $[PPN]_2[Fe_3CuI(CO)_9(CCO)]$: $a = 11.863$ (2) Å, $b = 14.248$ (4) Å, $c = 23.807$ (2) Å, $\alpha = 75.33$ (2)°, $\beta = 87.36$ (1)°, $\gamma = 88.02$ (2)°, $V = 3888$ (2) Å^3, space group $P\bar{1}$, $Z = 2$, $d_{calcd} = 1.548$ g/cm^3, $\mu = 14.21$ cm^{-1}, Mo radiation, $\lambda = 0.710\,73$ Å, 7467 reflections with $I > 2.58\sigma I$, $R_F = 0.038$ and $R_{wF} = 0.042$.

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The analogy between H$^+$ and CuL$^{+/0}$, L = neutral/−1 ligand, or AuL$^{+/0}$ has been noted and can be useful in cluster chemistry.[19] However, small differences in bond energies can change the nature of products obtained from reaction with H$^+$ as compared with CuL$^{+/0}$. As seen in eq 2, the reaction of I with H$^+$ leads to protonation of carbon and the loss of the ketenylidene structure.[2] Compound II may represent an analogue of the intermediate or transition state in the protonation reaction.

Very recently, [PPN]$_2$[Ru$_3$CuI(CO)$_9$(CCO)] was prepared in a manner similar to the synthesis of II.[20] Initial spectroscopic data suggest that copper caps the metal face opposite the ketenylidene ligand to give a tetrahedral CuRu$_3$ framework. Thus, the ruthenium ketenylidene exhibits similar chemistry for both CuL$^{+/0}$ and H$^+$ since both add to the ruthenium framework.

Acknowledgment. A.S.G. was supported by a research fellowship from the Great Lakes Pew Science Program. Additional support came from the NSF Synthetic Organometallic Chemistry Program. We thank Prof. David Phillips for information on the interaction of Cu(I) phosphine complexes with I.

Supplementary Material Available: Listings of crystal data, positional and thermal parameters, and bond angles and distances (9 pages); listing of observed and calculated structure factors for [PPN]$_2$[Fe$_2$CuI(CO)$_9$(CCO)] (44 pages). Ordering information is given on any current masthead page.

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(20) Anal. Calcd for Ru$_3$CuIC$_{84}$O$_{10}$H$_{62}$N$_2$P$_4$Cl$_2$: Ru, 15.57; Cu, 3.29; C, 51.80; H, 3.21. Found: Ru, 16.31; Cu, 3.25; C, 53.04; H, 3.38.

Interionic Contacts in Complex Ion Pairs Detected by Rotating-Frame Nuclear Overhauser Effects

Thomas C. Pochapsky* and Patricia M. Stone

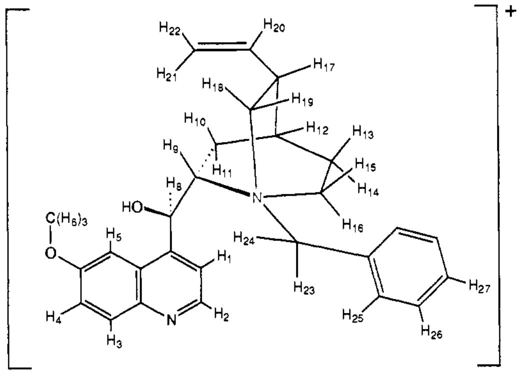
Department of Chemistry, Brandeis University
Waltham, Massachusetts 02254

Susan Sondej Pochapsky

Bruker Instruments, Inc., Manning Park
Billerica, Massachusetts 02181

Received October 18, 1990

The ion pair formed by reagent anion and lipophilic cation are thought to be the reactive species in phase-transfer reactions catalyzed by such cations.[1] As a member of an ion pair, an anion is carried across the phase boundary into nonpolar media in which it may react efficiently with nonpolar substrates. It has been noted that if an asymmetric cation is used as a phase-transfer catalyst, asymmetry is often induced in the products.[2] Information concerning the structure(s) of the ion pair formed in such cases would be valuable in determining the roots of the asymmetric induction and aid in the design of more effective asymmetric catalysts. Recently, we reported the observation of specific ^{1}H{^{1}H} and ^{11}B{^{1}H} nuclear Overhauser effects (NOE) to the BH$_4^-$ anion upon selective saturation of the proton resonances of the tetrabutylammonium ion in CDCl$_3$ solution.[3] We have attempted to extend the use of the interionic NOE to determining the structure and dynamics of more complex ion pairs, in particular, that formed by the 8α-9(*R*)-hydroxy-1-(phenylmethyl)cinchonanium ("benzylquininium" or BQ) and the tetrahydroborate ions, **1**, in CDCl$_3$ solution. The BQ ion has been used successfully as an asymmetric catalyst for the phase-transfer reduction of prochiral ketones by BH$_4^-$,[2] and so ion pair **1** seemed a reasonable point at which to begin these investigations. Unlike the case of the simple ion pair studied previously, however, driven steady-state presaturation NOE experiments on ion pair **1** yielded only a few very weak interionic NOEs which were difficult to interpret. This observation might be rationalized in a number of ways. The ion pair might be solvent-separated, and the lack of observable NOEs due to weak and/or nonspecific association between cation and anion. Alternatively, $\omega_c\tau_c$, the product of the correlation time and the transition frequency being considered, might be close to 1.12, in which case NOEs are not observed regardless of internuclear distance.[4] Generally, for molecules under MW 1000 in nonviscous solvents (short τ_c), this is not a concern. However, aggregation of ion pairs might increase the correlation time sufficiently that the apparent molecular weight of the ion pair is quite large, with concomitant loss of NOE intensity. In this case, interionic NOEs might still be observable when rotating-frame techniques are used (CAMELSPIN[5] or ROESY[6] experiments) in which the observed NOE is always positive and increases monotonically with τ_c.[7] In fact, significant NOEs are observed between the protons of BH$_4^-$ and specific BQ resonances in **1** in the rotating frame.



1

The ^{1}H spectrum of **1** was completely assigned by using a combination of COSY (*J*-correlated spectroscopy) and ROESY (rotating-frame NOE spectroscopy) data.[8,9,10] Unlike the spectrum of the ion pair studied previously,[3] the ^{1}H spectrum of **1** shows considerable concentration dependence, especially for the resonances of quinuclidine protons H$_9$, H$_{16}$, and H$_{18}$ and the benzyl

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(8) **1** was prepared by exhaustive treatment of a CH$_2$Cl$_2$ solution of the chloride salt of BQ, prepared by standard methods, with a concentrated basic aqueous solution of NaBH$_4$. Purity was determined by relative integrations of the BQ and BH$_4^-$ proton signals. NMR samples were prepared immediately prior to spectroscopy in deacidified CDCl$_3$. Samples used for NOE and ROESY experiments were freeze–thaw degassed. Two-dimensional phase-sensitive COSY spectra were obtained on the 500-MHz LDB-500 instrument built by A. Redfield and S. Kunz (Brandeis University). Two-dimensional phase-sensitive ROESY spectra were obtained on a 300-MHz AMX-300 instrument (Bruker Instruments). Data workup was performed by using D. Hare's FELIX program operating on a Silicon Graphics Iris workstation.

(9) For convenience we have used the proton numbering system of Dijkstra et al. for ease of comparison with the spectra of other quinine and quinidine derivatives (Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069–8076). Proton resonance assignments for **1** are as follows: (parts per million from TMS, 0.25 M at 25 °C): H$_1$ 7.68; H$_2$ 8.66; H$_3$ 7.92; H$_4$ 7.27; H$_5$ 7.20; H$_6$ 3.90; H$_8$ 6.62; H$_9$ 3.90; H$_{10}$ 1.48; H$_{11}$ 2.21; H$_{12}$ 1.98; H$_{13}$ 1.70; H$_{14}$ 2.26; H$_{15}$ 3.02; H$_{16}$ 4.58; H$_{17}$ 2.51; H$_{18}$ 3.60; H$_{19}$ 3.42; H$_{20}$ 5.61; H$_{21}$ 5.07; H$_{22}$ 4.94; H$_{23}$ 5.51; H$_{24}$ 4.77; H$_{25}$ 7.72; H$_{26}$ 7.33; H$_{27}$ 7.40; BH$_4^-$ 0.30.

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