studies, the hemoglobin structure.[14] The comparison of photoinitiated (^{3}Zn porphyrin) → (Fe^{III} porphyrin) electron transfer within the mixed-metal [Fe^{III}P,ZnD] and [Fe^{III}P,ZnP] hybrids presented here has permitted us to identify a direct role of vinyl groups in determining the transfer distance within a biological system where donor/acceptor *orientation* and intervening protein *medium* are *fixed*.

The [α(FeP),β(ZnD)] hybrid and ZnDHb were prepared by procedures analogous to those for the ZnP-containing proteins.[15] The optical spectrum of the [α(Fe^{II}P),β(ZnD)] hybrid exhibits two maxima in the Soret region, one for the Fe^{II}P at 430 nm and one for ZnD at 412 nm. Oxidation of the Fe^{II}P to Fe^{III}P yields a normal [(Fe^{III}(H$_2$O)P)–(Fe^{II}P)] static difference spectrum,[11c] and the resultant hybrid has a single, combined Soret peak at 412 nm. The band for ZnD within the hybrid and ZnDHb is blue-shifted relative to the ZnP band in the corresponding proteins, in agreement with the trends observed for a series of Zn metalloporphyrins.[16] Similarly, the phosphorescence emission maximum for ZnDHb at ambient is blue-shifted to 708 nm from the value of 720 nm for ZnPHb.

Flash excitation of the [Fe^{II}P,ZnD] hybrid produces the ^{3}ZnD state, which decays with a rate constant, $k_D = 50(5)\ s^{-1}$ (Figure 2), essentially the same as that for ^{3}ZnP within the analogous hybrid.[11] When the [Fe^{III}P,ZnD] hybrid is photolyzed, electron-transfer quenching increases the decay rate to $k_{obsd} = 85\ (10)\ s^{-1}$, which corresponds to a ^{3}ZnD → Fe^{III}(H$_2$O)P electron-transfer rate of $k_t(\text{ZnD}) = k_{obsd} - k_D = 35\ (10)\ s^{-1}$. This compares with an observed rate of $k_{obsd} = 150\ (10)\ s^{-1}$ for the [Fe^{III}(H$_2$O)P,ZnP] hybrid,[11c] which corresponds to $k_t(\text{ZnP}) = 100\ (10)\ s^{-1}$ (Figure 2). Arguments presented elsewhere show that the measurement is not the result of spin or energy-transfer quenching;[11c] indeed the blue-shift of the ^{3}ZnD emission relative to that of ^{3}ZnP increases any spectral overlap with Fe^{III}P and would *increase* the quenching rate if Fe–Zn energy transfer were important, contrary to observation. Thus, elimination of the vinyl group on the ^{3}Zn-porphyrin donor through use of ZnD rather than ZnP reduces the nonadiabatic[11b] electron-transfer rate at ambient temperature by a factor of $k_t(\text{ZnP})/k_t(\text{ZnD}) \equiv \gamma \approx 2.8$.[17]

Figure 2 also presents Arrhenius plots of k_t for the [Fe^{III}(H$_2$O)P,ZnP] and [Fe^{III}(H$_2$O)P,ZnD] hybrids; for comparison, the scale of $\ln[k_t(\text{ZnP})]$ is shifted by a constant amount of -0.85. The points for the ZnP and ZnD hybrids as plotted in this way clearly overlap, and the small activation energies obtained by least-squares fits agree within experimental error: $\Delta E^*(\text{ZnD}) = 0.06\ (5)$ eV; $\Delta E^*(\text{ZnP})$[11b] $= 0.10\ (5)$ eV.[18] Thus, $k_t(\text{ZnD})$ is reduced from $k_t(\text{ZnP})$ by a change in the temperature-independent, electron-tunnelling preexponential term for the rate constant.[1]

The present results show that a vinyl group of a ^{3}ZnP donor can conjugate with the ring sufficiently well to serve as an electron-transfer antenna. The preexponential factor of the rate constant[1] for nonadiabatic electron transfer is suggested to represent a weighted contribution from the electron densities on all conjugated atoms,[4] and we may write the following: $k_t(\text{ZnP}) = k_t(\text{vinyl}) + k_t(\text{other})$; $k_t(\text{ZnD}) = k_t(\text{other})$.[13] Even though the electron density associated with a conjugated vinyl moiety is small,[13] the value, $\gamma \approx 2$–3, as seen in Figure 2, implies that the term associated with the shortest distance between redox centers, k_t(vinyl), represents over $^2/_3$ of the measured rate for the [Fe^{III}(H$_2$O)P,ZnP] hybrid. This suggests that often it will be a good approximation to discuss long-range electron-transfer measurements in terms of a single parameter, the distance of closest approach between conjugated atoms. In fact, Gray and co-workers[3] conclude that the rate constant can be described in terms of a single distance (d), with $k_t \propto \exp(-0.9d)$. This would predict $k_t(\text{ZnP})/k_t(\text{ZnD}) = \exp(0.9\Delta d) \sim 2.5$ for $\Delta d \sim 1$ Å, in accordance with our experiments.

Acknowledgment. We thank Drs. J. Fajer, L. K. Hanson, and N. Sutin for helpful discussions, G. Martin for able assistance in the preparation of hybrids, and Prof. J. Torkelson for the use of his phosphorimeter. This work has been supported by NIH Grant HL 13531 and NSF Grant DMG 8606575 (B.M.H.) and by NIH,NRSA Fellowship HL07531 to M.J.N.

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(14) Seybert, D. W.; Moffat, K. *J. Mol. Biol.* **1976**, *106*, 895–902.

(15) (a) For preparation of [α(FeP),β(ZnD)], β-chain globin was reconstituted with ZnD and mixed with α(FeCO) chains in a modification of the method of Waterman and Yonetani (ref 15b). ZnDHb was prepared by modifications of procedures described in ref 15c. Detailed procedures will be described elsewhere. (b) Waterman, M. R.; Yonetani, T. *J. Biol. Chem.* **1970**, *245*, 5847–5852. (c) Scholler, D. M.; Wang, M. R.; Hoffman, B. M. In *Methods in Enzymology*; Fleischer, S., Packer, L., Eds.; Academic Press: New York, 1978; Vol. 52, part C, pp 487–493.

(16) Wang, M. Y. R.; Hoffman, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 4235–4240.

(17) We note that the observation of a substantial change in rate for the ZnD hybrid indicates that the electron-transfer process in the [Fe,Zn] hybrids is not gated by a conformational conversion. See: Hoffman, B. M.; Ratner, M. A. *J.* Am. *Chem. Soc.*, in press.

(18) (a) This is consistent with the negligible differences in reduction potentials for ZnD$^+$ and ZnP$^+$ (ref 18b) and in triplet state energies measured on a Spex 1934C phosphorimeter: $\Delta E_T(\text{ZnPHb}) = 1.72$ eV and $\Delta E_T(\text{ZnDHb}) = 1.75$ eV. (b) Stanienda, A.; Biebl, G. *Z. Phys. Chem. (Frankfurt am Main)* **1967**, *52*, 254–275.

Total Synthesis of a C$_{15}$ Ginkgolide, (±)-Bilobalide

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Cambridge, Massachusetts 02138

Received July 23, 1987

The ginkgo tree, *Ginkgo biloba*, which has existed in its present form for thousands of centuries, produces a collection of unusual polycyclic structures (ginkgolides) which are C$_{15}$[1] and C$_{20}$[2] polylactones.[3] Extracts of the ginkgo, which have long been recommended in Chinese medicine, are now commonly used in Europe for the treatment of cerebrovascular and peripheral circulatory problems of the elderly. Reported herein is the first total synthesis of a member of the ginkgolide family (±)-bilobalide (**1**), a C$_{15}$-trilactone.

Enone **2**, which contains all the carbon atoms needed for the synthesis of **1**, was prepared by a remarkably simple, single-step process.[4] Reaction of the dilithio derivative of dimethyl *cis*-4-cyclohexen-1,2-dicarboxylate[5] in THF containing 3 equiv of hexamethylphosphoric triamide with 1 equiv of phenyl 3-*tert*-butylpropiolate[6] at −45 °C for 30 min and 0 °C for 4 h produced after extractive isolation and silica gel (sg) chromatography enone **2** in 72% yield.[7] Reduction of **2** with sodium borohydride in 1:1.5 methanol–isopropyl alcohol at 0 °C for 7 h furnished stereoselectively allylic alcohol **3** (75%). Ozonolysis of **3** at −78 °C in 1:1 methylene chloride–methanol containing 5 equiv of sodium bicarbonate, reduction of the intermediate with dimethyl sulfide, and extractive isolation gave aldehyde lactol **4** in 80% yield. The acetal **5**[8] was obtained from **4** by treatment with 0.05 equiv of p-toluenesulfonic acid in 5:1 methanol–methyl orthoformate at 23 °C for 24 h (72% after sg chromatography in the presence of

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(1) Nakanishi, K.; Habaguchi, K.; Nakadaira, Y.; Woods, M. C.; Maruyama, M.; Major, R. T.; Alauddin, M.; Patel, A. R.; Weinges, K.; Bähr, W. *J. Am. Chem. Soc.* **1971**, *93*, 3544–3546, and references contained therein.

(2) (a) Sakabe, N.; Takada, S.; Okabe, K. *J. Chem. Soc., Chem. Commun.* **1967**, 259–261. (b) Okabe, K.; Yamada, S.; Yamamura, S.; Takada, S. *J. Chem. Soc. C* **1967**, 2201–2206. (c) Nakanishi, K. *Pure Appl. Chem.* **1967**, *14*, 89–113.

(3) The ginkgo tree, remarkably resistant to pests, especially fungi, can continue to reproduce up to an age of over 1000 years: Major, R. T. *Science (Washington, D.C.)* **1967**, *157*, 1270–1273. A giant 3000 year old ginkgo with a trunk measuring 15.8 meters stands at Dinglin Temple near Juxian, Shandong, China.

(4) An independent but longer synthesis of **2** has been accomplished by using previously described intermediates. See: Corey, E. J.; Su, W-g.; Houpis, I. N. *Tetrahedron Lett.* **1986**, *27*, 5951–5954.

(5) All reactions involving air-sensitive reagents or reactants were conducted under an atmosphere of dry nitrogen or argon.

(6) Synthesized from *tert*-butylacetylene by sequential treatment in ether solution with n-butyllithium and phenyl chloroformate at −20 °C. See: Tashner, M. J.; Rose, T.; Heathcock, C. H. *Org. Synth.* **1985**, *64*, 108–113.

(7) Other examples of this novel annulation are described in a separate publication: Corey, E. J.; Su, W-g. *Tetrahedron Lett.*, in press.

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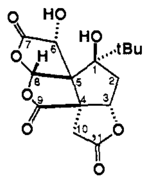
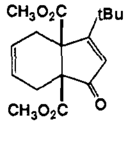


1



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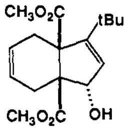
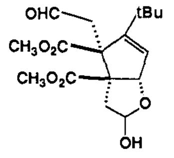
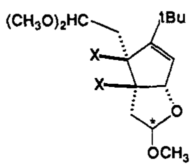


3



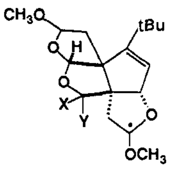
4



5 X = CO$_2$CH$_3$

6 X = CH$_2$OH

7 X = CHO

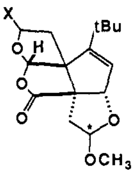


8a X = H, Y = OH

8b X = OH, Y = H

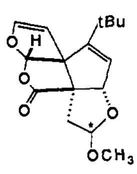
9 X,Y = O

triethylamine, as two anomers in a 4:1 ratio; TLC R_f values 0.42 and 0.40, respectively, with use of 1.5:1 hexane–ethyl acetate). Reduction of **5** using lithium aluminum hydride in ether at 0 °C for 1 h gave diol **6** which upon Swern oxidation in methylene chloride with 3 equiv of oxalyl chloride and 6 equiv of dimethyl sulfoxide at −45 °C followed by 8 equiv of triethylamine and warming to 23 °C produced dialdehyde **7**. Treatment of **7** with THF containing 1% of 1 N hydrochloric acid at 0 °C for 1 h caused cyclization to a mixture of epimeric lactols **8a** and **8b** which without purification was oxidized with 4 equiv of pyridinium dichromate and 50 equiv of acetic acid in methylene chloride in the presence of powdered 4Å molecular sieves at 23 °C for 5 h to give lactone **9**[8] in 80% yield. Exposure of **9** to 1:1:20 1 N aqueous potassium hydroxide–THF–ethanol at 23 °C for 12 h effected selective replacement of methoxy by hydroxyl via γ-lactone hydrolysis and subsequent opening of the 2,5-dioxygenated tetrahydrofuran ring to give after acidification and isolation **10**,[8] mp 125–127 °C, in 90% yield.[9] Reaction of **10** with 1.5 equiv of methanesulfonyl chloride and 2 equiv of triethylamine at −30 °C for 30 min and then at 23 °C for 2 h provided the isolable chloro ether **11** (purified by sg chromatography with use of 5% ethyl acetate and 1% of triethylamine in hexane as eluent) which was transformed into vinyl ether **12**[8] (mp 124–128 °C, 83% yield from **10**) by reaction with 2 equiv of diisopropylethylamine in acetonitrile at reflux for 12 h. Epoxidation of **12** with 10 equiv of peroxy-3,5-dinitrobenzoic acid in methylene chloride in the presence of excess sodium bicarbonate at 23 °C for 36 h generated the remarkably stable diepoxide **13**,[8] isolated in 95% yield after sg chromatography with use of 10% ethyl acetate in hexane for elution.[10] The epoxidation is stereospecific at each double bond, the assigned stereochemistry as in **13** following from ^{1}H NMR

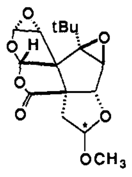


10 X = OH

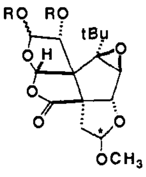
11 X = Cl



12

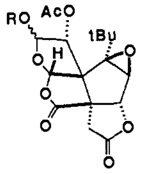


13



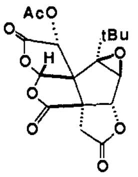
14 R = H

15 R = Ac



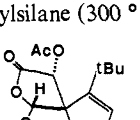
16 R = Ac

17 R = H

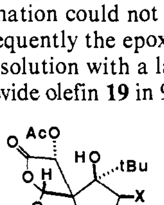


18

data and from conversion of **13** to bilobalide (**1**).[11] Treatment of diepoxide **13** with 1:5 0.5 N aqueous hydrochloric acid–THF at 60 °C for 3 h afforded a diol (**14**, configuration at C(7) unassigned) which upon acetylation (10 equiv of acetic anhydride, 4 equiv of 4-(dimethylamino)pyridine in methylene chloride at 23 °C for 4 h) gave diacetate monolactone **15**[8] ($J_{6,7}$ 6.0 Hz) in 89% yield from **13**. Reaction of **15** with a solution of 7 equiv of peroxy-3-chlorobenzoic acid and 3 equiv of boron trifluoride etherate in 20:1 methylene chloride–ether at 60 °C for 12 h produced dilactone **16** (92%)[12] which was converted to trilactone **18** (96% overall) in two steps: (1) hydrolysis (1:1:6 0.5 N hydrochloric acid–acetic acid–THF at 80 °C for 3 h) to form lactol **17** and (2) oxidation (4 equiv of pyridinium dichromate in methylene chloride at 23 °C for 4 h) to afford **18**. Although hydrogenolysis of the C(2)–O bond of epoxide **18** could produce bilobalide, in practice this transformation could not be realized under a variety of conditions. Consequently the epoxide **18** was deoxygenated by heating in toluene solution with a large excess of triethylsilane (300 °C, 36 h) to provide olefin **19** in 90% yield.[13]



19



20 X = OH

21 X = OCOCO$_2$CH$_3$

22 X = H

Synthetic (±)-**19** was identical with the known anhydro bilobalide acetate[1] (**19**), produced by the action of acetic anhydride containing a trace of sulfuric acid on bilobalide, by ^{1}H NMR, infrared, MS, and sg TLC (several solvent systems) comparison. Reaction of synthetic **19** with osmium tetroxide and pyridine in ether at 23 °C for 12 h produced a single diol **20**, mp 86–88 °C, spec-

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[8] Compound obtained as a 4:1 mixture of anomers at the starred carbon, which stereocenter is removed subsequently in the conversion of **15** to **16**.

[9] All compounds for which mp's are not reported herein were obtained as oils.

[10] Epoxidation of **12** with 1 equiv of peroxy-3-chlorobenzoic acid led to selective epoxidation of the *trisubstituted* olefinic bond rather than the vinyl ether linkage. It is clear that the carboxylate substituent on the dihydrofuran ring strongly removes electron density from the oxygen of the furan ring. This effect accounts not only for the diminished nucleophilicity of the vinyl ether unit in **12** but also the unusual solvolytic stability of chloro ether **11** and diepoxide **13**.

[11] The β-orientation of 1,2-epoxide in **13** is clearly indicated by the observed ^{1}H NMR $J_{2,3}$ coupling constant of 0 Hz.

[12] Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *20*, 419–422.

[13] This method of conversion of a highly functionalized epoxide to the corresponding olefin, which to our knowledge is novel, probably proceeds by a radical chain mechanism involving attack by triethylsilyl on the oxirane oxygen to form olefin and triethylsilyloxy as key propagation steps.

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troscopically and chromatographically identical with a sample of **20** produced in the same way from bilobalide-derived **19**. Synthetic diol **20** was converted to bilobalide 6-acetate (**22**) by a two-step process: (1) reaction with methyl oxalyl chloride (1.3 equiv) and diisopropylethylamine (2 equiv) in acetonitrile at 0 °C for 2 h to form **21** in 100% yield and (2) reaction in dilute toluene solution at reflux with a low concentration of tri-*n*-butyltin hydride (3 equiv of a 0.05 M solution in toluene containing 0.05 equiv of azobisisobutyronitrile added by syringe drive over 4 h) to give the (±)-bilobalide acetate **22**, mp 270–274 °C (55%), along with recovered diol **20** (30%).[14] Synthetic (±)-**22** was identical with an authentic sample of bilobalide acetate[1] by 500-MHz ^{1}H NMR, infrared, mass spectral, and TLC comparison. Hydrolysis of synthetic (±)-**22** with 3 N hydrochloric acid at reflux for 36 h afforded (±)-bilobalide **1** (70% yield), spectroscopically and chromatographically identical with an authentic sample.[15] The synthesis of (±)-bilobalide described above solves one of the classical problems of organic synthesis by the use of novel chemistry and highly selective reactions. The one-step synthesis of **2** is both unprecedented and practical. In addition the conversions **7** → **9**, **9** → **12**, **12** → **13**, **18** → **19**, and **19** → **1** are noteworthy. The unusual *tert*-butylcarbinol unit of **1** greatly complicates the task of synthesis because the conventional methods of synthesis are inapplicable.[16]

Supplementary Material Available: Spectral and analytical data for **1–3**, **5–7**, **9a**,**9b**, **10–16**, and **17–22** (3 pages). Ordering information is given on any current masthead page.

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[14] See: Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588–1589. It is essential that the tin hydride be added slowly, otherwise the production of diol **20** increases relative to **22**.

[15] We are grateful to Dr. Pierre Braquet, Institute Henri Beaufour, Le Plessis Robinson, France, for a generous sample of naturally derived bilobalide.

[16] This research was assisted financially by a grant from the National Science Foundation.

Photoreactions of Group 6 Metal Carbonyls with Ethene: Syntheses of *trans*-(η^2-Ethene)$_2$M(CO)$_4$ (M = Cr, Mo, W)

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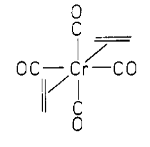
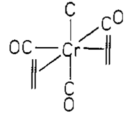
Photolysis of Cr(CO)$_6$ in ethene-doped liquid xenon at −78 °C has been reported[1] to yield (η^2-ethene)Cr(CO)$_5$ (**1a**), *trans*-(η^2-ethene)$_2$Cr(CO)$_4$ (**2a**), and *cis*-(η^2-ethene)$_2$Cr(CO)$_4$ (**3a**). All three compounds were said to be thermally unstable under these experimental conditions, their stability decreasing in the order **1a** > **2a** > **3a**. More recently[2] **1a** was photochemically generated from Cr(CO)$_6$ and ethene in the gas phase. Subsequent pulsed-laser photolysis produced a transient species, detected by means of time-resolved IR spectroscopy, which decayed on the ms time scale and was assigned as *cis*-(η^2-ethene)$_2$Cr(CO)$_4$ (**3a**). The lability and cis structure of **3a** was set in contrast with the stability and trans configuration of the known (η^2-olefin)$_2$M(CO)$_4$ complexes of molybdenum and tungsten.[3,4]

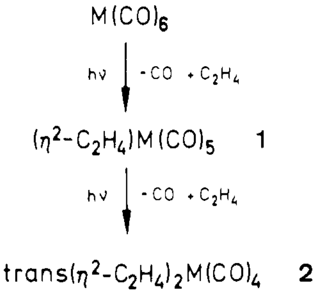


2a (D_{2d})



3a

Scheme I[a]



[a] M = Cr (**1a**, **2a**), Mo (**1b**, **2b**), W (**1c**, **2c**).

Table I. Spectroscopic and Analytical Data of **2a–c**

	2a	2b	2c
$\bar{\nu}$(CO),[a] cm^{-1}	≃1986 (vw) 1952.5 (vst)	1997.5 (vw) 1965 (vst)	1991 (vw) 1965 (vst)
δ (^{1}H)[b]	2.27	2.33	2.11
δ (^{13}C{^{1}H})[b] C$_2$H$_4$	48.25	41.89	31.26
CO	220.44	208.74	198.08
C found (calcd)	43.42 (43.65)	36.45 (36.38)	27.86 (27.30)
H	3.62 (3.66)	3.16 (3.05)	2.09 (2.29)
metal	23.72 (23.62)	36.21 (36.33)	52.32 (52.23)

[a] In *n*-hexane. [b] In toluene-d_8.

This conflicts with our experience with olefin-substituted group 6 metal carbonyls[3,5–7] and led us to suspect that the apparent disconformity should not be associated with the particular metal but rather originates from differences in the reaction conditions, i.e., gas-phase photochemistry in the chromium case[2] vs photoreactions of the molybdenum and tungsten compounds in solution.[3,4,6,7] Recent experiments allow us to expand on this point and prompt us to report on the photoreaction of Cr(CO)$_6$ with ethene in alkane solution, which provides convenient preparative access to the *stable trans*-(η^2-ethene)$_2$Cr(CO)$_4$ (**2a**).

Irradiation of Cr(CO)$_6$ (10 mM) in ethene-saturated pentane solution (solidex immersion well apparatus, λ ≥ 280 nm; Philips HPK 125-W mercury lamp) leads to sequential photosubstitution of CO for ethene; Scheme I, M = Cr. As monitored by infrared spectroscopy,[8] initially formed **1a** [$\bar{\nu}$(CO) = 2078 (w), 1967 (st), 1961.5 (vst) cm^{-1}][9] is largely converted into *trans*-(η^2-ethene)$_2$Cr(CO)$_4$ (**2a**)[9] upon extended irradiation. The first step is most conveniently performed at −20 °C, whereas the second step requires cooling to −50 °C. After filtration of the concentrated solution over silica gel and recrystallization from pentane, pure **2a** is obtained as pale yellow crystals, mp 67–68 °C, 30% yield.

Relevant spectroscopic and analytical data on **2a** are summarized in Table I. The observation of only one strong CO stretching vibrational band in the IR spectrum immediately rules out a *cis*-(η^2-ethene)$_2$Cr(CO)$_4$ structure [**3a**; four IR active ν(CO) vibrations] in favor of the *trans*-(η^2-ethene)$_2$Cr(CO)$_4$ geometry, most probably with orthogonal orientation of the two ethene ligands [D_{2d} symmetry; ν(CO): a$_1$ (IR inactive), b$_2$ (formally IR active, but extremely weak), e (IR active, very strong)]. This has been confirmed by the X-ray structure analysis of **2a**.[10] The ^{1}H and ^{13}C{^{1}H} NMR spectra (Table I) exhibit only one and two signals, respectively, in accordance with structure **2a**.

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[9] The IR data of **1a** and **2a** are in good agreement with those obtained in liquid xenon.[1]

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