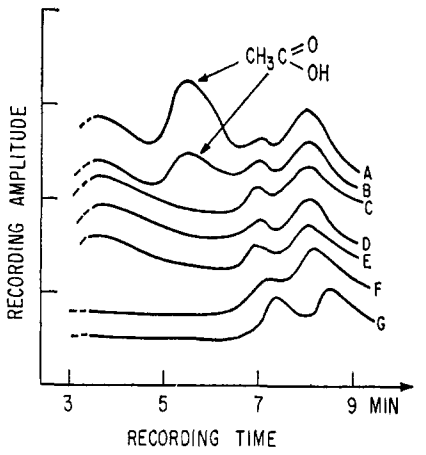
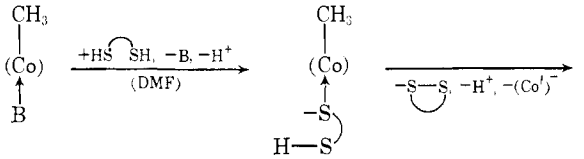
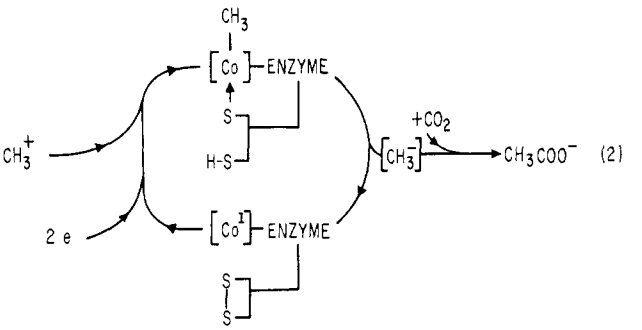



Figure 1. Gas–liquid partition chromatography tracings demonstrating acetic acid formation from methyl(pyridine)cobaloxime in DMF under the experimental conditions outlined in the text: (A) complete system, with added acetic acid as internal standard (0.01 mmol/ml); (B) complete system without added acetic acid; (C) system as in (A), but after treatment with solid NaOH; (D) system as in (B) after treatment with solid NaOH; (E) system as in (B) but run under argon instead of $CO_2$; (F) system as in (E) but with ethyl(pyridine)cobaloxime; (G) complete system with ethyl-(pyridine)cobaloxime. Measurements were performed with a 5-ft Poropak Q column at 22 cc/min He flow rate, with $H_2$ flame detector. All measurement tracings were obtained at attenuation 2.

*e.g.*, pyridine]. To verify eq 1 in a nonenzymatic model system methylcobaloximes were reductively cleaved with dithioerythritol in aqueous solution under 1 atm of $CO_2$. Although the main product was methane as




expected, acetic acid was nevertheless detected in yields up to 0.01% of the total cobaloxime. To increase the acetate formation the reaction was conducted in anhydrous dimethylformamide (DMF) with 1,4-butanedithiol as the reducing agent. Under these more favorable conditions, a 50-fold yield increase was observed, affording acetic acid in amounts of up to 1% of the methylcobaloxime present initially. In a specific experiment 1 mmol of methyl(pyridine)cobaloxime was dissolved in 4 ml of anhydrous DMF. After displacing the air in the reaction vessel by 1 atm of $CO_2$, 2 mmol of 1,4-butanedithiol was added and the reaction mixture was maintained at 65° for 12 hr. Analysis of the liquid phase was performed by glpc using a 5-ft Poropak Q column, as well as a 5-ft 5% FFAP column for separation and comparison with an authentic sample. The acetic acid peak disappears on treating the reaction solution with dilute NaOH and is absent if the reactions are run under argon. It is also not observed if ethyl- and *n*-propylcobaloximes are treated with $CO_2$ in the presence of thiols under similar conditions (Figure 1). We therefore conclude that a reaction analogous to eq 1 could occur enzymatically, provided that the active site is maintained in a locally aprotic environment. The available evidence indeed suggests that a thioprotein is involved in the acetate formation at least of *C. thermoaceticum*. Thus, the conversion of methylcobalamin to acetate is inhibited[2] by iodoacetamide, 4-iodoacetylsalicylic acid, and other typical sulfhydryl group blocking reagents. Assuming that one of the terminal steps in the acetate synthesis consists in the transfer of labile methyl groups to the reduced corrin cofactor, the essential steps in the enzymatic reactions can be summarized by eq 2, where [Co] denotes the corrin.




The mechanism in eq 2 has the advantage of having been directly verified by plausible model experiments and that no specific $CO_2$ activation is required. It furthermore relates the corrin-dependent acetate biosynthesis to methane biosynthesis and ribonucleotide reduction.[9] All three enzymatic processes are corrin dependent and utilize thioredoxin systems in the terminal electron transfer reactions.

(9) J. W. Sibert and G. N. Schrauzer, *J. Amer. Chem. Soc.*, **92** 1421 (1970).

(10) This research was supported by Grant No. GP12324 of the National Science Foundation.

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## Syntheses of [2.2]Metacyclophane-1,9-diene and *trans*-15,16-Dihydropyrene

*Sir:*

The question of whether *trans*-15,16-dihydropyrene is capable of a finite existence is a long standing one. Neunhoeffer and Woggon suggested the possibility of 15,16-dihydropyrene being present in solutions from metal reductions of pyrene,[1] but this could not be confirmed,[2] and later work by Gerson, Heilbronner, Reddoch, Paskovich, and Das showed that the Birch reduction of pyrene gives two isomeric tetrahydropyrenes from which the corresponding radical is exceptionally stable.[3] Although various *trans*-15,16-dialkyldihydropyrenes have now been known for some time,[4–6] the ease of thermal rearrangement of *trans*-15,16-dialkyldihydropyrenes,[7] particularly with larger alkyl groups,[6] also raised the possibility that *trans*-

(1) O. Neunhoeffer and H. Woggon, *Angew. Chem.*, **68**, 386 (1956); *cf. Justus Liebigs Ann., Chem.*, **600**, 34 (1956).
(2) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *J. Amer. Chem. Soc.*, **83**, 943 (1961).
(3) F. Gerson, E. Heilbronner, H. A. Reddoch, D. H. Paskovich, and N. C. Das, *Helv. Chim. Acta*, 50, 813 (1967).
(4) V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, **89**, 1695 (1967).
(5) V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).
(6) V. Boekelheide and T. A. Hylton, *ibid.*, in press.
(7) V. Boekelheide and E. Sturm, *ibid.*, **91**, 902 (1969).

15,16-dihydropyrene might have a rather transient existence.

Nevertheless it seemed worthwhile to investigate this question and interest in doing so was strongly stimulated by our recent discovery of a convenient new method for the synthesis of *trans*-15,16-dimethyldihydropyrene.[8] This method, involving the transformation of a sulfide linkage into a carbon–carbon double bond, allows the synthesis of substituted [2.2]metacyclophane-1,9-dienes under mild and carefully controlled conditions. For the present study, 2,11-dithia[3.3]metacyclophane (**1**) was prepared in 48% yield by the reaction of *m*-xylylene dibromide and sodium sulfide.[9] Treatment of **1** with dimethoxycarbonium fluoroborate[10] gave the corresponding bissulfonium salt (**2**) in quantitative yield as white crystals, mp 200° dec.[11] The Stevens rearrangement of **2** was complete in 5 min using potassium *t*-butoxide in tetrahydrofuran and gave a mixture of the *cis* and *trans* isomers, **3** and **4**, in a ratio of 1:4 and in an overall yield of 93%.

The mixture of the *trans* isomers (**4**) was readily separated from the mixture of *cis* isomers (**3**) by chromatography over silica gel. The assignment of *trans* geometry to **4** is based on the fact that the nmr spectrum of this mixture shows the signal for the "internal protons" in the range of $\tau$ 4.4–5.7, as expected for *trans*-[2.2]metacyclophanes,[12] whereas the nmr spectrum of **3** is in accord with *cis* geometry in that the signal for the "internal protons" appears in the normal aromatic region.[13]

Methylation of the *trans* mixture (**4**) with dimethoxycarbonium fluoroborate in methylene chloride at −30° again proceeded in quantitative yield to give the bissulfonium salt **5**. This, on treatment with potassium *t*-butoxide in tetrahydrofuran at 0°, effected elimination of dimethyl sulfide. The neutral hydrocarbon fraction from this reaction proved to be a mixture of pyrene (**8**) and [2.2]metacyclophane-1,9-diene (**6**). Careful chromatography of this mixture over silica gel using hexane gave [2.2]metacyclophane-1,9-diene (**6**) in 35% yield as colorless crystals, mp 119–120°. The assignment of structure to **6** is based on its spectral data, its hydrogenation in quantitative yield to *trans*-[2.2]metacyclophane, and its conversion to *trans*-15,16-dihydropyrene. The mass spectrum of **6** shows the parent molecular ion at 204 with strong peaks at 203 and 202, corresponding to the loss of one and two hydrogens. The ultraviolet spectrum of **6** shows a single broad absorption band at 280 nm ($\epsilon$ *ca.* 28,000). Analysis of the nmr spectrum of **6** in carbon tetrachloride shows a singlet at $\tau$ 2.10 (2 H, $H_x$), an $AB_2$ multiplet at 2.99 (2 H, $H_a$), an $AB_2$ multiplet at 3.40 (4 H, $H_b$), and a singlet at 3.78 (4 H, $H_c$).

The isolation and purification of *trans*-[2.2]metacyclophane-1,9-diene (**6**) are remarkable in view of the fact that all of the 8,16-dialkyl[2.2]metacyclophane-1,9-dienes undergo spontaneous valence tautomerization at room temperature to the corresponding *trans*-15,16-dialkyldihydropyrenes.[6,14] In contrast, **6** appears to be stable indefinitely when stored under nitrogen at room temperature in the crystalline state.

When a sample of **6** was sealed under high vacuum, dissolved in degassed cyclohexane, and irradiated with light at 2537 nm, the solution quickly turned deep green. The nmr spectrum of this solution is presented in Figure 1 (A) and corresponds to a mixture of *trans*-15,16-dihydropyrene (**7**) and pyrene (**8**). By computer the pyrene absorption can be subtracted from the experimental spectrum and a simulated spectrum for *trans*-15,16-dihydropyrene results as shown in Figure 1 (B). The signal for $H_c$ appears as a singlet at $\tau$ 1.42, $H_b$ as a doublet at 1.50 ($J$ = 7.5 Hz), $H_a$

(8) R. H. Mitchell and V. Boekelheide, *Tetrahedron Lett.*, 1197 (1970).

(9) The preparation of 2,11-dithia[3.3]metacyclophane has been described previously (T. Sato, M. Wakabayashi, M. Kainosho, and K. Hata, *ibid.*, 4185 (1968), and F. Vögtle and L. Schunder, *Chem. Ber.*, **102**, 2677 (1969)) and Sato gives its melting point as 155.5–156.5°. Our sample melts at 120–121° and since it has the correct elemental composition, mass spectrum, and an nmr spectrum in agreement with that reported, we assume our sample to be simply a different crystalline modification from that of Sato.

(10) R. F. Borch, *J. Org. Chem.* 34, 627 (1969).

(11) Satisfactory analytical data have been provided for all new compounds except *trans*-15,16-dihydropyrene which has not been isolated in a pure state. Likewise, all new volatile compounds show parent molecular ions in their mass spectra in accord with the assigned structures.

(12) D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Amer. Chem. Soc.*, 82, 6302 (1960).

(13) The mixture of **4** has been separated into four individual isomers and **3** has been separated into two individual isomers. The description of these separations and the properties of the individual isomers will be presented elsewhere.

(14) H.-R. Blattmann, D. Meuche, E. Heilbronner, R. J. Molyneux, and V. Boekelheide, *J. Amer. Chem. Soc.*, 87, 130 (1965).

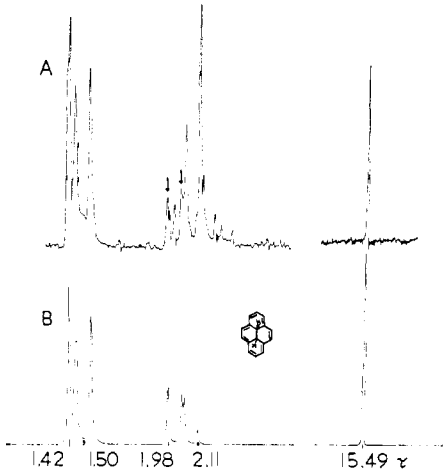


Figure 1. (A) The experimental nmr spectrum of *trans*-15,16-dihydropyrene (**7**) in cyclohexane. The signal in the region of 2.0 is due to the presence of pyrene with the underlying signals from **7** marked by arrows. B is a computer simulated nmr spectrum for **7** in which the signals due to pyrene have been subtracted from the experimental spectrum in A. Spectra recorded with a Varian HA-100 MHz spectrometer.

as a multiplet at 1.98–2.11, and $H_x$ as a singlet at 15.49. In view of the fact that $H_x$ is allylic, this is a remarkable upfield chemical shift, a proof of the strong diamagnetic ring current, and the aromatic nature of **7**. Further, the visible spectrum of **7** is very similar to that of the other *trans*-15,16-dihydropyrenes.

Although such sealed, degassed cyclohexane solutions of **7** appear to be reasonably stable in the dark at room temperature, prolonged exposure to light at 2537 nm leads to a clean conversion to pyrene. Similarly, exposure of such solutions to oxygen leads to a rapid, but not instantaneous, conversion to pyrene. Finally, when such solutions are heated the intensity of the green color is lessened and this occurs very rapidly at temperatures above 60°. Although the structures of these thermal rearrangement products have not yet been established, they are presumably the result of a 1,5-sigmatropic rearrangement of the hydrogens from the interior to the periphery.[7] In retrospect, it is remarkable that **7** is so stable at room temperature and does not spontaneously undergo such a 1,5-sigmatropic rearrangement.

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## Syntheses of Novel Tris-Bridged Cyclophanes. [2.2.2](1,3,5)Cyclophane-1,9,17-triene

*Sir:*

Recently, we reported on a method for the transformation of a sulfide linkage to a carbon–carbon double bond.[1] This has provided a convenient synthesis for *trans*-15,16-dimethyldihydropyrene,[1] both

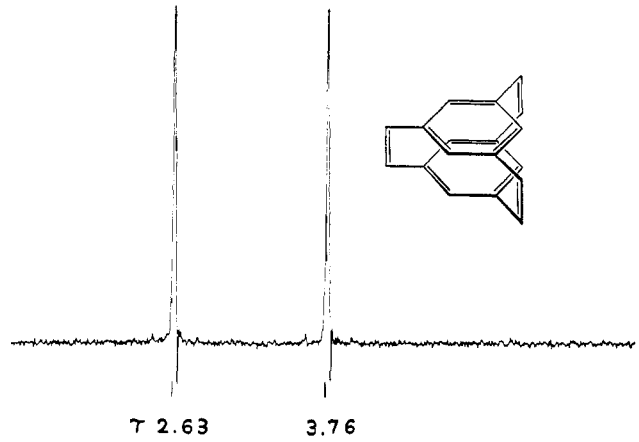


Figure 1. The nmr spectrum of [2.2.2](1,3,5)cyclophane-1,9,17-triene (**6**) in deuteriochloroform measured with a Varian 60-MHz spectrometer.

*trans*-[2.2]metacyclophane-1,9-diene and *trans*-15,16-dihydropyrene,[2] and [2.2]metaparacyclophane-1,9-diene.[3] Recent nmr studies provide evidence that the *cis* and *trans* conformers of 2,11-dithia[3.3]metacyclophane interconvert rapidly at room temperature.[4] In view of this it seemed possible that a suitably substituted derivative of 2,11-dithia[3.3]metacyclophane might undergo ring closure and be locked in a *cis* conformation. We now report the successful experimental test of this hypothesis and the consequent synthesis of 2,11,20-trithia[3.3.3](1,3,5)cyclophane, **2**. Furthermore, application of our method of transforming sulfide linkages to olefinic bonds has led to the conversion of **2** to the unusual tris-bridged cyclophane **6**.[5]

When 1,3,5-tris(bromomethyl)benzene (**1**) was treated with sodium sulfide in ethanol under the standard conditions for such reactions,[2] it was converted in 12% yield to 2,11,20-trithia[3.3.3](1,3,5)cyclophane (**2**), isolated as white crystals, mp 254–255°.[6] Treatment of **2** with dimethoxycarbonium fluoroborate[7] gave the tris-sulfonium salt (**3**) as fine white needles, but as a mixture of isomers, in 100% yield. This mixture was treated directly with sodium hydride in tetrahydrofuran to effect a triple Stevens rearrangement and to give the tris-sulfide **4** as a mixture of isomers in 38% yield. This, in turn, was again treated with dimethoxycarbonium fluoroborate to give the tris-sulfonium salt **5** in 100% yield. When **5** was suspended in ether at −78° and treated with *n*-butyllithium, it was converted to the desired triene **6** in 5% yield, isolated as white platelets, mp 203–204°, after recrystallization from petroleum ether (30–60°).

The nmr spectrum of **6** (see Figure 1) shows only two singlets of equal intensity at $\tau$ 2.63 and 3.76. In view of the fact that **6** represents a rigid molecule in

(1) R. H. Mitchell and V. Boekelheide, *Tetrahedron Lett.*, 1197 (1970).

(2) R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, **92**, 3510 (1970).

(3) V. Boekelheide and P. H. Anderson, *Tetrahedron Lett.*, 1207 (1970).

(4) T. Sato, M. Wakabayashi, M. Kainosho, and K. Hata, *ibid.*, 4185 (1968).

(5) Although tris-bridged cyclophanes have been reported previously (see D. J. Cram and R. A. Reeves, *J. Amer. Chem. Soc.*, **80**, 3094 (1958), and A. J. Hubert, *J. Chem. Soc. C*, 6, 10, 13 (1967)), these are the first examples where the bridges involve only two linking atoms.

(6) The empirical formulae of all new compounds have been substantiated by elemental analyses and/or high resolution mass spectra.

(7) R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).