We have established that the aromatic product formed quantitatively from the enzymatic processing of **1** is *p*-methylbenzoate,[7] indicating a complete diversion from the normal reaction pathway leading to aldehyde. Moreover, no irreversible inactivation of BFD has been detected.

We believe that these results constitute a novel example of enzyme-catalyzed halide elimination and inhibition of a TPP-dependent enzyme. Decarboxylation and bromide ion elimination from the enzyme-bound adduct formed from TPP and **1** (**2**; Scheme II) would generate the quinone-like **3**. This intermediate may undergo either enzyme-catalyzed or chemical tautomerization to yield (*p*-methylbenzoyl)-TPP (**4**). In the presence of excess TPP dissociation of **4** from BFD would permit an unmodified TPP to "rescue" the enzyme, resulting in a remarkably rapid turnover determined by the dissociation constant (k_{off}) for **4**.[8] Without excess TPP turnover of **1** is evidently dependent upon the hydrolysis of **4**. Since BFD does not normally catalyze hydrolysis of an acyl-TPP, turnover without excess TPP is ultimately determined by this process, which must be relatively slow.[9]

Leung and Frey[10] have reported that 3-fluoropyruvate undergoes decarboxylation, fluoride elimination, and tautomerization by pyruvate dehydrogenase; on the other hand, 3-chloro- and 3-bromopyruvate appear to be much more complex in their reactions with this enzyme.[11] Also, Kuo and Jordan[12] have found that (*E*)-4-(4-chlorophenyl)-2-keto-3-butenoic acid functions as an irreversible (Michael-type) inhibitor of pyruvate decarboxylase. Our findings are somewhat reminiscent of the inactivation of γ-aminobutyric acid transaminase by gabaculine.[13] In that case, covalent modification of pyridoxal was achieved by aromatization of the gabaculine–pyridoxal adduct via an enzyme-catalyzed tautomerization.

Enzyme-catalyzed eliminations of halide ion through an intervening phenyl group are intriguing phenomena which have been proposed for the formation of quinone–methide intermediates by bioreductive alkylating agents.[14] The present study constitutes a clear example of this process by a carbanionic elimination.[15]

Acknowledgment. This work was supported by USPHS Grants GM 35066 and GM 35067 (J.W.K.) and AM 17323 and CA 37655 (G.L.K.). L.J.D. gratefully acknowledges an NSF Predoctoral Fellowship (1981–1984) and is a Ph.D. candidate at Yale University. We thank Paul Weiss and Dr. Paul F. Cook for help with preliminary experiments. We also thank Dr. Frank Jordan for a sample of (*E*)-4-(4-chlorophenyl)-2-keto-3-butenoic acid.

(7) An ethereal extract of an acidified, completed reaction mixture was treated with diazomethane. The resulting methyl *p*-toluate was identified and quantitated by comparison with an authentic sample, using gas chromatography–mass spectrometry.

(8) These results suggest that $k_{off} \sim 0.5\ s^{-1}$. The reported Km for TPP is 1 μM.[1]

(9) We estimate that $k_{hydrolysis} \sim 1\ min^{-1}$. While this rate is slow relative to the other enzymatic rate constants, it agrees well with the reported instability of 2-benzoyl-3,4-dimethylthiazolium iodide, an analogue of **4**, to hydrolysis and methanolysis: White, F. G.; Ingraham, L. L. *J. Am. Chem. Soc.* **1962**, *84*, 3109.

(10) Leung, L. S.; Frey, P. A. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 274. In contrast, our preliminary studies show that [*p*-(fluoromethyl)-benzoyl]formate is a normal substrate for and not an inhibitor of BFD. This suggests that the intervening phenyl group imposes an energy barrier sufficient to prevent fluoride but not bromide elimination. The chloro analogue is currently under study.

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Tris(benzocyclobutadieno)benzene, the Triangular [4]Phenylene with a Completely Bond-Fixed Cyclohexatriene Ring: Cobalt-Catalyzed Synthesis from Hexaethynylbenzene and Thermal Ring Opening to 1,2:5,6:9,10-Tribenzo-3,4,7,8,11,12-hexadehydro[12]-annulene

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1,3,5-Cyclohexatriene is commonly introduced in organic textbooks as the hypothetical model for a bond-fixed benzene, yet the search for this structural unit has been elusive.[1] We report two facile approaches to the tris(benzocyclobutadieno)benzene nucleus **1**, including the parent **1b**, in which the central benzene ring exists in this form, and the first thermal retrocycloaddition of a benzene ring to a trialkyne. Our strategy relies on an iterative sequence of palladium-catalyzed alkynylations followed by cobalt-catalyzed cyclobutabenzoannelations.[2]

The simplest approach to **1** is outlined in Scheme I and involves the also theoretically interesting hexaethynylbenzene (**2**)[3] as an intermediate and its 3-fold cyclization in which a record number (for cobalt) of six rings and nine bonds are formed to give what must be an extraordinarily strained molecule.[4] Protodesilylation then furnishes the title compound **1b**.[5] Scheme II depicts a stepwise approach to the title compound, providing chemical structural corroboration, support for a stepwise cyclization path in Scheme I, and another derivative of **1**.[5] It starts with bis(2-bromophenyl)ethyne (**3**)[6] which was converted to the corresponding diiodide **4**[7] (necessary for the success of the subsequent step), subsequently to be subjected to a novel palladium-catalyzed

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(5) All new compounds gave satisfactory analytical and/or spectral data. For example, **1a**: yellow crystals (from acetone), mp (acetone solvate) >315 °C; MS, *m/e* (relative intensity) 732.3295 (M^+, 49, calcd for $C_{42}H_{60}Si_6$ 732.3311), 119 (15), 73 (100); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.42 (s, 36 H), 2.16 (s, acetone, 6 H), 7.53 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 2.33, 125.50, 131.23, 147.56, 148.88; IR (KBr), 2960, 2905, 1750 (acetone), 1270, 1253, 1067, 850, 753, 653 cm^{-1}; UV (hexane) λ_{max} 242 (log ϵ = 4.72), 251 (4.79), 291 (4.90), 299 (5.09), 314 (5.33), 347 (4.47), 364 (4.33), 376 sh (4.21), 394 sh (4.06) nm. **1b**: yellow crystals, mp 248 °C; MS/ *m/e* (relative intensity) 300.0937 (M^+, 100, calcd for $C_{24}H_{12}$ 300.0939), 272 (22); ^1H NMR (300 MHz, acetone-d_6) δ 7.24 (AA′ m, 6 H), 7.31 (BB′ m, 6 H); (250 MHz, $CDCl_3$) δ 7.19 (s); ^{13}C NMR ($CDCl_3$) δ 119.79, 128.63, 130.13, 148.44; IR (KBr), 3050, 2920, 1775, 1760, 1451, 1432, 1358, 1167, 1120, 750, 732, 697 cm^{-1}; UV (hexane) λ_{max} 227 sh (log ϵ = 4.22), 234 (4.39), 243 (4.56), 269 (4.38), 282 (4.61), 297 (4.85), 324 sh (3.91), 336 (4.02), 352 (3.90), 363 sh (3.7), 379 sh (3.4) nm. **4**: colorless crystals, mp 103 °C. **5**: colorless crystals, mp 174–175 °C; MS, *m/e* (relative intensity) 418.1571 (M^+, 100, calcd for $C_{28}H_{26}Si_2$ 418.1573), 73 (22); ^1H NMR (200 MHz, $CDCl_3$) δ 0.26 (s, 18 H), 7.34 (m, 4 H), 7.50 (m, 2 H), 7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −0.39, 75.22, 78.21, 88.02, 91.88, 92.23, 123.99, 127.00, 128.23, 128.86, 132.33, 132.75; IR (KBr) 2970, 2210, 2107, 1490, 1253, 1040, 860, 760 cm^{-1}. **6**: yellow crystals, mp 186 °C; MS, *m/e* (relative intensity) 418.1572 (M^+, 100, calcd for $C_{28}H_{26}Si_2$ 418.1573), 73 (30); ^1H NMR (200 MHz, $CDCl_3$) δ 0.27 (s, 18 H), 7.00 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 0.07, 99.80, 100.3, 119.2, 119.5, 129.36 (2C), 134.1, 147.8, 149.8, 149.0, 152.5; IR (KBr) 2142 cm^{-1}; UV (cyclohexane) λ_{max} 235 (log ϵ = 4.53), 247 (4.53), 280 (4.70), 293 (4.82), 305 (4.51), 314 (4.37), 320 (4.37), 331 (4.62), 398 (3.53), 422 (3.58), 452 (3.51) nm. **1c**: yellow crystals, mp 239 °C.

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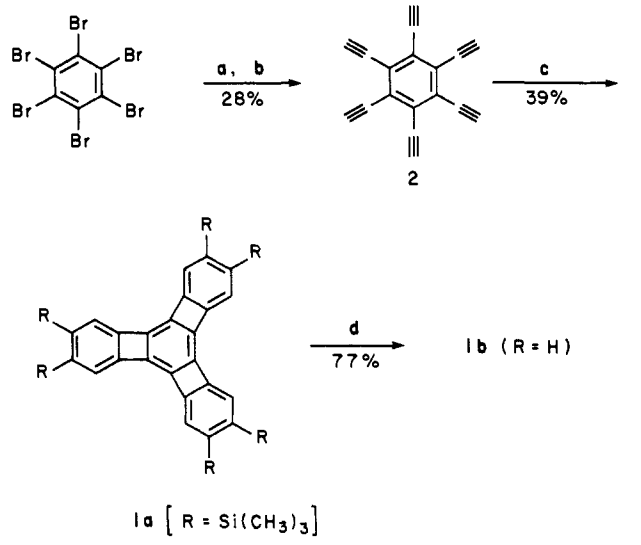
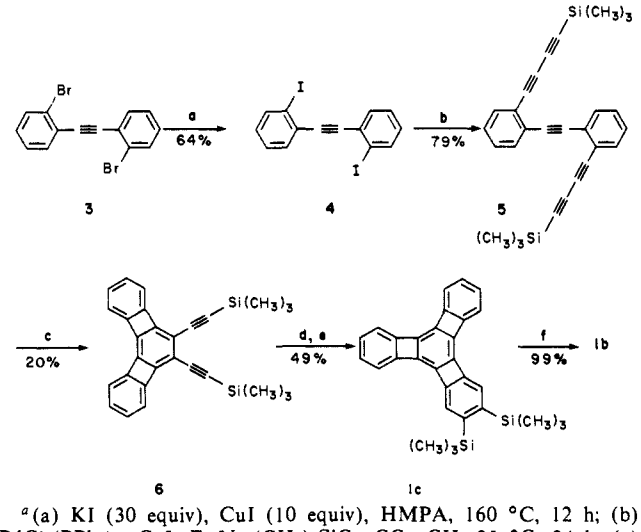
Scheme I[a]



[a] (a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, $(CH_3)_3SiC{\equiv}CH$, 100 °C, 72 h; (b) $KF{\cdot}2H_2O$, 18-crown-6, glyme, 10 min; (c) $CpCo(CO)_2$, $(CH_3)_3SiC{\equiv}CSi(CH_3)_3$, Δ, 19.5 h; (d) CF_3COOH, $CHCl_3$, 14 h.

Scheme II[a]



[a] (a) KI (30 equiv), CuI (10 equiv), HMPA, 160 °C, 12 h; (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, $(CH_3)_3SiC{\equiv}CC{\equiv}CH$, 25 °C, 24 h; (c) $CpCo(CO)_2$, *o*-xylene, Δ, 7 h; (d) KOH, CH_3OH, 1 h; (e) $CpCo(CO)_2$, $(CH_3)_3SiC{\equiv}CSi(CH_3)_3$, Δ, 9 h; (f) CF_3COOH, $CHCl_3$, 12 h.

coupling with (trimethylsilyl)butadiyne.[2] The resulting pentayne **5** was cyclized by catalytic $CpCo(CO)_2$ to the first derivative **6** of the angular [3]phenylene.[8] Deprotection and renewed cyclization furnished **1c**, which proved to be readily protodesilylated to **1b**.[5]

Tris(benzocyclobutadieno)benzene **1b** is expected to show high bond localization in the central benzene ring because the system is anticipated to minimize benzocyclobutadiene character. Indeed, the spectral data provide preliminary evidence for that expectation, revealing unusually shielded ^{13}C NMR peaks ($\Delta\delta \sim -18$) for the central carbons, ^1H NMR chemical shifts for the outside benzenes close to normal, and UV absorptions at considerably higher energy than those of the isomeric linear [4]phenylene,[9] suggesting *cis*-stilbene-like conjugation. In order to put a quantitative structural measure on this point an X-ray investigation was carried out on **1a** (Figure 1).[10]

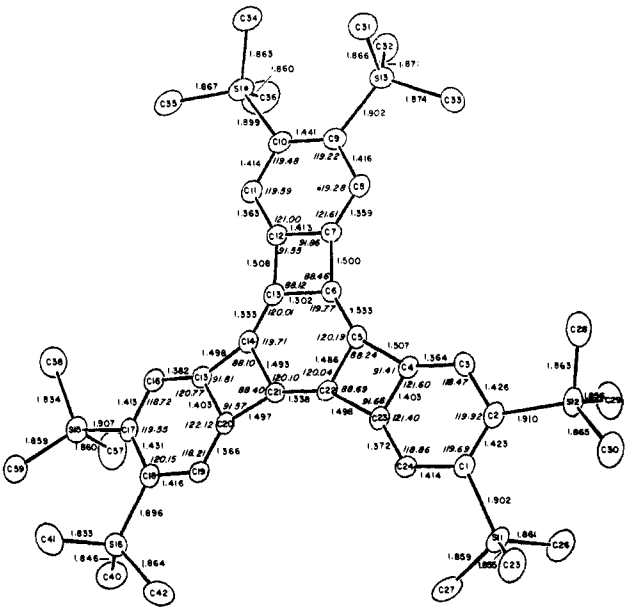


Figure 1. ORTEP drawing of **1a** (acetone solvate not shown). Ellipsoids are scaled to represent the 50% probability surface. Bond lengths are in angstroms, angles in degrees (italics).

Due to crystal packing forces and the strain incorporated in the *o*-bis(trimethylsilyl) units, the molecule is neither completely planar nor symmetrical. However, its structural features are corroborated by this analysis. Most striking is the relatively small degree of bond fixation in the oustide rings, comparable to that in 4,5-bis(trimethylsilyl)benzocyclobutene,[11] biphenylene,[12] and angular [3]phenylene,[13] and the extraordinary extent of bond localization in the central ring, amounting essentially to the presence of single and double bonds,[2,14] more localized than in ordinary conjugated 1,3-dienes.[15] There is no doubt that **1** incorporates a nondelocalized (or maximally localized) cyclohexatriene unit.

The thermal stability of **1** is surprising in light of the extremely strained character of the system.[4] MMP2 calculations predict that the (unprecedented) thermal retrocyclization to the isomeric triyne 5,6,11,12,17,18-hexadehydrotribenzo[*a,e,i*]cyclododecene (1,2:5,6:9,10-tribenzo[3,4,7,8,11,12-hexadehydro[12]annulene)[16] should be *exothermic* by 58 kcal mol^{-1}. Although experiments show that the barrier to thermal [2 + 2 + 2] cycloaddition (and therefore also the reverse) of three alkyne units to a benzene ring

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(10) Crystal size 0.3 × 0.4 × 0.5 mm, monoclinic Laue symmetry, space group *I2/a*, a = 26.597 (4) Å, b = 14.0062 (14) Å, c = 29.1233 (19) Å, β = 112.451 (9)°, V = 10027 (4) Å^3, μ_{calcd} = 2.00 cm^{-1}, d_{calcd} = 1.16 g cm^{-3}, radiation Mo K_α (λ = 0.71073 Å), scan range 3° ≤ 2θ ≤ 45°, reflections collected at −113 (4) °C, 7218, unique 4824 with $F^2 > 3\sigma(F^2)$, R = 4.43%, R_w = 5.97%.

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is prohibitive[17] (theoretical calculations[18] place barriers between 62 and ~80 kcal mol^{-1} on this transformation), the strained nature of **1** suggests that it should be able to undergo ring opening to the triyne. Indeed, while **1b** is stable in the neat state to 400 °C (10 min, 50% recovery), flash pyrolysis (700 °C, 10^{-2} mm) leads to the desired isomerization (40%; clearly identifiable by spectral data, paticularly ^{13}C NMR[20]). This retrocyclization is the first which unravels a benzene ring to its three-component alkyne units in a purely thermal process without additional reagents which would be normally required to overcome thermodynamic obstacles.[19] Our observations lend support to the contention that **1b** may have been an intermediate in the flash-thermolytical decomposition of a tricinnoline to the same triyne.[20]

With **1b** and two of its derivatives at hand, a detailed investigation of their physical, chemical, and physiological properties will be the subject of future efforts.

Acknowledgment. This paper is dedicated to the memory of Carol L. Goodman, who died after a heroic battle with life. This work was supported by the National Institutes of Health (CA-20713); K.P.C.V. is a Miller Research Professor in Residence (1985-1986). R.D. was the recipient of a NATO Science Fellowship (1984-1985). The X-ray structural analysis was carried out by Dr. F. J. Hollander, staff crystallographer. We thank J. C. Armstrong for carrying out the pyrolysis experiments on **1b**.

Supplementary Material Available: A listing of positional and thermal parameters and tables of bond lengths and angles and structure factors for **1a** (45 pages). Ordering information is given on any current masthead page.

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Sterochemical Analysis of the Methyl Transfer Catalyzed by Cobalamin-Dependent Methionine Synthase from *Escherichia coli* B

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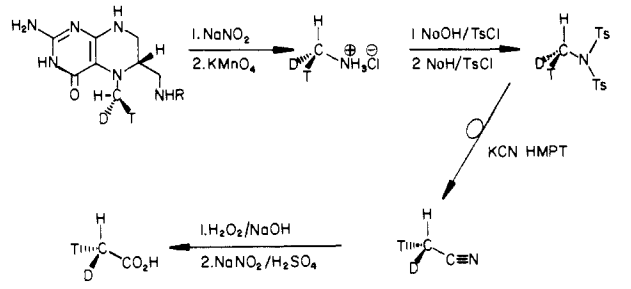
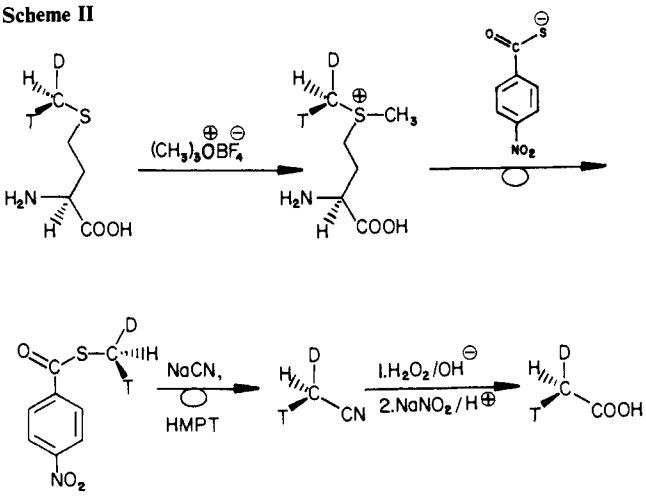
The last step in the biosynthesis of methionine involves transfer of the methyl group of N_5-methyltetrahydrofolate (5-CH_3-H_4-folate) or its polyglutamate analogue to the sulfur of homocysteine:

5-CH_3-H_4folate + $HSCH_2CH_2CH(NH_2)COOH$ → $CH_3SCH_2CH_2CH(NH_2)COOH$ + H_4folate

Scheme I



Scheme II



Two classes of methionine synthases are known to catalyze this reaction, one contains cobalamin as a cofactor and the other is cobalamin-independent.[1] The first class is found in mammalian tissues and the second class in plants, and microorganisms may have either one or both enzymes.

To further our understanding of the catalytic mechanism of methionine synthases, we studied the steric course of the methyl transfer from 5-CH_3-H_4folate to homocysteine catalyzed by the cobalamin-dependent enzyme from *E. coli*. The requsite substrate, 5-CH_3-H_4folate, carrying a chiral methyl group, was prepared by sequential reduction of 5,10-methenyltetrahydrofolate (5,10-CH^+-H_4folate) with NaB^2H_4 in the presence of diethylaniline, known to produce monodeuterated 5,10-methylenetetrahydrofolate (5,10-CH_2-H_4folate) with over 80% stereoselectivity,[2] followed by further reduction of the 5,10-CH_2-H_4folate with a 2-fold excess of tritiated sodium borohydride in 50 mM Tris buffer, pH 7.5[3] (Scheme III). The diastereomer of opposite methyl configuration was generated from 5,10-CH_2-H_4folate produced by $NaBH_4$ reduction of 11-deuterio-5,10-CH^+-H_4folate. The 5-CH_3-H_4folate was purified by passage over a column of DEAE Sephadex and elution with a linear gradient of 0.2-2.0 M triethylammonium bicarbonate. Fractions containing 5-CH_3-H_4folate were pooled and concentrated by lyophilization. The two samples of 5-CH_3-H_4folate were degraded by diazotation and $KMnO_4$ oxidation to give methylamine[4,5] which by standard procedures[6] was converted stereospecifically to acetic acid for chirality analysis[7-9] of

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[‡]Pennsylvania State University.
[§]University of Michigan.

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