2644 *J. Am. Chem. Soc.* **1992**, *114*, 2644-2652

Multifaceted Consequences of Holding Two [8]Annulene Rings Face-to-Face. Synthesis, Structural Characteristics, and Reduction Behavior of [2$_2$](1,5)Cyclooctatetraenophane

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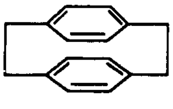
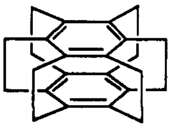
Abstract: The doubly-decked [8]annulene **11** has been prepared in 13 steps from the known diketone **15**. The scheme takes advantage of the annulating capacity of the Cook–Weiss reaction and the ability of semibullvalenes to undergo thermal isomerization to cyclooctatetraenes. The bis(semibullvalene) **12** is both conformationally dynamic and subject to very rapid Cope rearrangement. The energetics of inversion within its interconnective cyclooctane ring have been elucidated by variable-temperature ^{1}H NMR spectroscopy. The structural nature of **11** has been made clear by a combination of molecular mechanics calculations and X-ray crystallography. Also, the reduction chemistry associated with **11** has been examined in anhydrous HMPA at room temperature and in dry Me$_2$NH between 208 and 253 K. The tetraanion was produced at the lowest operating temperature. The structural changes that occur during electron transfer have been deduced from the *E* values and heterogeneous kinetics. Finally, the response of **11** to Diels–Alder cycloaddition has been probed with *N*-phenylmaleimide as the dienophile.

Extensive exploitation of highly strained cyclophanes containing benzene rings as decks[1] has revealed that the onset of π–π repulsion[2] and the extent of distortion from planarity[3] can be considerable when the interconnective bridges are short. [2.2]-Paracyclophane (**1**) and superphane **2**[4] are notable examples.



1



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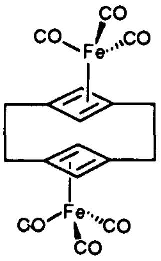

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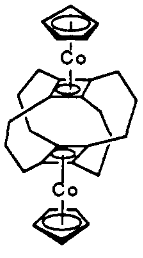
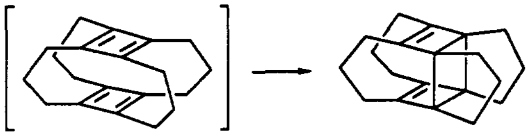


4

Photoelectron spectroscopic studies have revealed orbital interaction between the two aromatic rings in **1** to give rise to an electronic splitting of approximately 1 eV.[5]

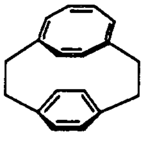
These observations have led to theoretical inquiries into the consequences of bridging two antiaromatic $4n$ π-electron systems into close proximity for the purpose of achieving mutual stabilization. Calculations involving pentalene and indacene predict that an interdeck distance of approximately 2.4 Å could bring about stabilization.[6] The involvement of two cyclobutadiene moieties at comparable levels of proximity can also possibly lead to charge transfer, such that an orbital splitting amounting to an energy lowering of more than 50 kcal/mol could materialize.[5]

These impressive predictions have encouraged Adams[7] and Gleiter[8] to prepare the cyclobutadienophanes **3** and **4**, respectively. When the metal atoms were released from **4**,[8] intramolecular cycloaddition occurred in **5** to deliver **6**. Unfortunately, direct examination of superphane **5** appears to be prohibited by the high reactivity of the compound.



5 **6**

Boekelheide was the first to appreciate the fact that enforced face-to-face proximity of a cyclooctatetraene (COT) unit against a benzene ring as in **7** and **8** could provide important information regarding electron delocalization in cyclophanes having decks with both $4n$ and $(4n + 2)$ π-electrons.[9] However, the tub-shaped geometry of the COT ring in these molecules (established crystallographically) permits interaction exclusively between the benzene ring and only one isolated double bond.



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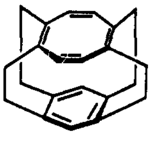

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When both decks are constructed of COT rings, the opportunity for examining a greater range of chemical and physical phenomena

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‖ Albert-Ludwigs-Universität.

(1) (a) Keehn, P. M., Rosenfield, S. M., Eds. *Cyclophanes*; Academic Press: New York, 1983; Vols. 1 and 2 and references cited therein. (b) Boschke, F. L., Ed. *Topics in Current Chemistry*; Springer-Verlag: New York, 1983; Vols. 113 and 115 and references cited therein. (c) Greenberg, A., Liebmann, J. F., Eds. *Strained Organic Molecules*; Academic Press: New York, 1978; Vol. 38 and references cited therein.

(2) Klostner-Jensen, E.; Wirz, J. *Helv. Chim. Acta* **1975**, *58*, 162.

(3) Hoppe, H.; Bernstein, J.; Trueblood, K. N. *Acta Crystallogr. Sect. B* **1972**, *28*, 1733.

(4) (a) Sekine, Y.; Brown, M.; Boekelheide, V. *J. Am. Chem. Soc.* **1979**, *101*, 3126. (b) Sekine, Y.; Boekelheide, V. *J. Am. Chem. Soc.* **1981**, *103*, 1777.

(5) (a) Boschi, R.; Schmidt, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 402. (b) Heilbronner, E.; Maier, J. P. *Helv. Chim. Acta* **1974**, *57*, 151. (c) Pignaturo, S.; Mancini, J. N. A.; Ridyard, N. A.; Lempka, H. *J. Chem. Soc., Chem. Commun.* **1971**, 142.

(6) Böhm, M. C.; Bickert, P.; Hafner, K.; Boekelheide, V. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 2589.

(7) Adams, C. M.; Holt, E. M. *Organometallics* **1990**, *9*, 980.

(8) (a) Gleiter, R.; Karcher, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 840. (b) Gleiter, R.; Karcher, M.; Ziegler, M. L.; Nuber, B. *Tetrahedron Lett.* **1987**, *28*, 195.

(9) Garbe, J. E.; Boekelheide, V. *J. Am. Chem. Soc.* **1983**, *105*, 7384.

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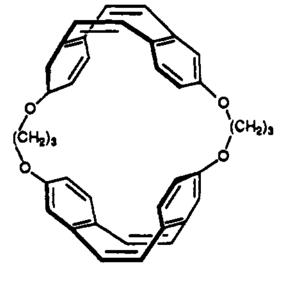
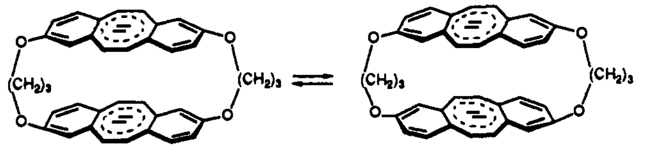
is made available. Müllen recently prepared the dibenzo-fused compound **9** and recognized that the size of the intraring cavity was substantially altered upon reduction.[10] The resulting tetraanion is assumed to be a statistical mixture of the rapidly interconverting meso and *dl* forms **10′** and **10″**. This and related multiply-charged intermediates offer unusual opportunities for metal complexation.

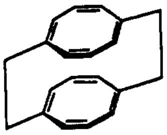


9



10′ **10″**

Unfortunately, compound **9** is too heavily substituted to answer many interesting questions dealing with intradeck bond shifting dynamics, cycloaddition behavior, and associated chemical phenomena. These limitations are lifted when parent cyclooctatetraenophanes such as **11** are considered. For this reason, a versatile synthetic route to this previously unknown class of compounds has been developed, the details of which are presented here for the first member of the series.[11] Crystallographic evidence for the preferred relative positioning of the double bonds in **11** is also reported along with a complete isodynamical profile. Finally, the reduction chemistry of this structurally unusual cyclophane has been examined in depth.

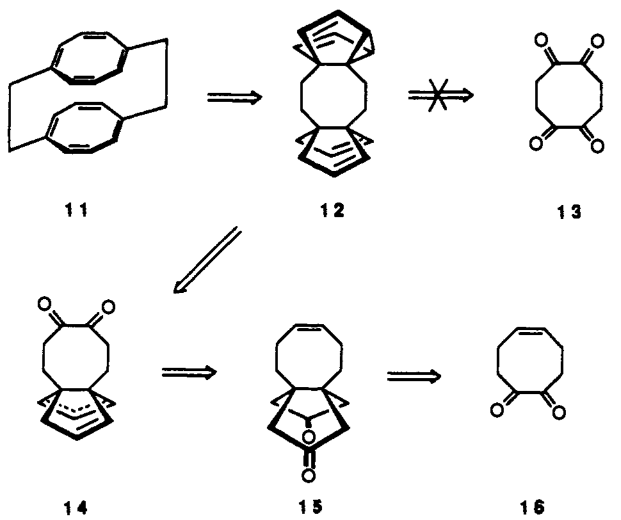


11

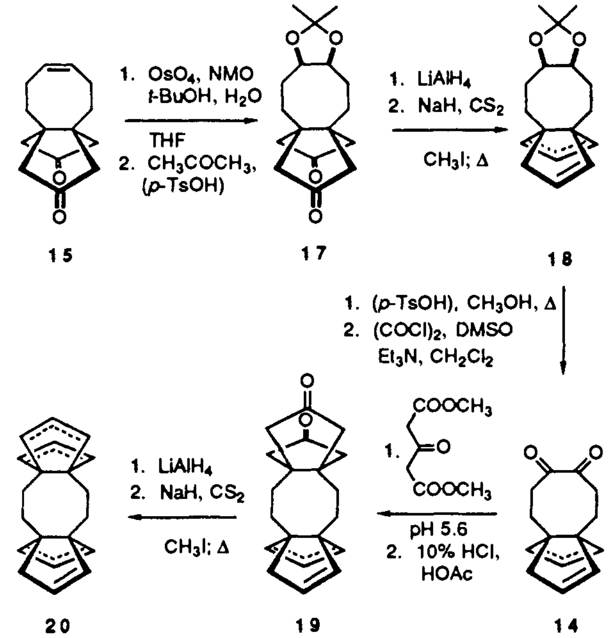
Results and Discussion

Cyclooctatetraenophane Synthesis. From among the limited number of valence isomerization methods available for the elaboration of cyclooctatetraene frameworks,[12] that based on the thermal rearrangement of semibullvalenes[13] was considered most adaptable to the present circumstances. As shown in Scheme I, efficiency would be particularly well served if **11** were to be directly derived from **12**, with constitutional isomerization occurring in two unsaturated regions of the hydrocarbon. Our past experience with the construction of simpler polymethylene-bridged cyclooctatetraenes along similar lines[14] suggested that **12** might be achieved by application of the Cook–Weiss reaction[15] to a suitably oxidized cyclooctane derivative. Continued adherence to the tandem functionalization plan would require that the retrosynthetic analysis consider tetraketone **13** as the starting material. However, this substance remains unknown to the present time, could be laborious to prepare,[16] and most importantly, could prove sensitive to the condensation conditions required for the elaboration of **12**. For these reasons, attention was given instead to advancing to **12** in stepwise fashion, particularly since the [6.3.3]propellenedione **15** was recognized to be readily available[17] from *cis*-5-cyclooctene-1,2-dione (**16**).[18]

Scheme I



Scheme II



Success was ultimately to depend on our ability to deal properly with the differing types of functionality necessarily present in both sectors of **15**. To this end, the synthesis began by catalytic osmylation of **15** followed by direct conversion to acetonide **17** (Scheme II). The plan was further implemented by sequential $LiAlH_4$ reduction and double Chugaev elimination. Although several isomers of the rather water-soluble diol are possible, the

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[10] Heinz, W.; Räder, H.-J.; Müllen, K. *Tetrahedron Lett.* **1989**, *30*, 159.

[11] Preliminary communication: Paquette, L. A.; Kesselmayer, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 1258.

[12] Paquette, L. A. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; Jai Press, Inc.: Greenwich, CT, in press.

[13] (a) Paquette, L. A.; Russell, R. K.; Wingard, R. E., Jr. *Tetrahedron Lett.* **1973**, *19*, 1713. (b) Russell, R. K.; Wingard, R. E., Jr.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 7483. (c) Paquette, L. A.; Ley, S. V.; Meisinger, R. H.; Russell, R. K.; Oku, M. *J. Am. Chem. Soc.* **1974**, *96*, 5806.

[14] (a) Paquette, L. A.; Trova, M. P. *Tetrahedron Lett.* **1987**, *28*, 2795, errata 4354. (b) Paquette, L. A.; Trova, M. P.; Luo, J.; Clough, A. E.; Anderson, L. B. *J. Am. Chem. Soc.* **1990**, *112*, 228.

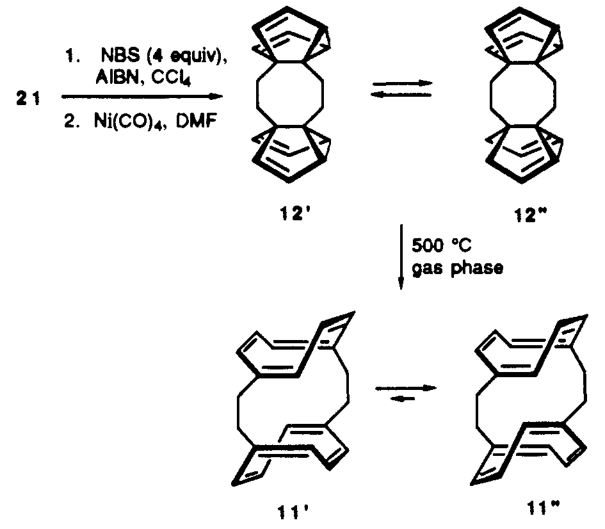
[15] Review: Gupta, A. K.; Fu, X.; Snyder, J. P.; Cook, J. M. *Tetrahedron* **1991**, *47*, 3665.

[16] (a) Cava, M. P.; Ratts, K. W. *J. Org. Chem.* **1962**, *27*, 752. (b) McIntyre, D.; Proctor, G. R.; Rees, L. *J. Chem. Soc. C* **1966**, 985. (c) Yates, P.; Lewars, E. G.; McCabe, P. H. *Can. J. Chem.* **1970**, *48*, 788.

[17] Mitschka, R.; Oehldrich, J.; Takahashi, K.; Cook, J. M. *Tetrahedron* **1981**, *37*, 4521.

[18] Yates, P.; Lewars, E. G.; McCabe, P. H. *Can. J. Chem.* **1972**, *50*, 1548.

Scheme III



major diastereomer could be easily separated and characterized. In turn, dihydrosemibullvalene **18** was obtained as a relatively high-melting compound, despite its acquisition as an inseparable mixture of two double bond regioisomers. Since both of these ketals are to converge to a single intermediate at a later stage, their co-formation is not of long-range consequence.

Mild acidic hydrolysis and subsequent Swern oxidation afforded **14**. This means of producing the α-diketone was found to occur with a minimum of overoxidation or cleavage, as has been encountered frequently in other contexts.[19] In accord with expectation, 2-fold annulation of **14** via the Cook–Weiss reaction served admirably well to generate the pivotal pentacyclic diketone efficiently (85%). The conversion of **19** into **20** by the same two-step sequence used previously on **17** was accomplished without event. The highly insoluble nature of the intermediate diol is noteworthy.

The targeted bis(semibullvalene) **12** was reached in practical amounts by initially subjecting **20** to 4-fold allylic bromination (Scheme III). This quadruple functionalization process operated most efficaciously when the mixture containing 4 equiv of *N*-bromosuccinimide and a catalytic quantity of AIBN in CCl_4 was heated for only 20 min. The resulting product mixture was then directly exposed to nickel carbonyl in DMF[14b] for the purpose of reductive coupling. This reagent system afforded **12** in 34% isolated yield.

The 300-MHz ^1H NMR spectrum of **12** (in $CDCl_3$) is characterized by four downfield triplets centered at δ 5.16, 4.99, 4.18, and 4.09 (J = 3.8 Hz in each instance). This simplicity, which is also reflected in the ^{13}C NMR spectrum, is testimony to the highly fluxional character of both divinylcyclopropane partial structures in this tetraene. In actuality, this spectrum is more complicated than usual. Thus, semibullvalene itself[20] and simple derivatives thereof[21] are characterized by only two absorptions for the same four protons because of a bisecting mirror plane (C_s symmetry). Anet et al. have recently pointed out that fusion of a cycloalkane ring to C(1) and C(5) of a semibullvalene promotes rigidification about the commonly shared ring-juncture positions, such that the lowest energy conformation of the adjacent ring approximates that of the cycloalkene equivalent.[22] In the present example, 1,5-cyclooctadiene serves as the point of reference.[23] On

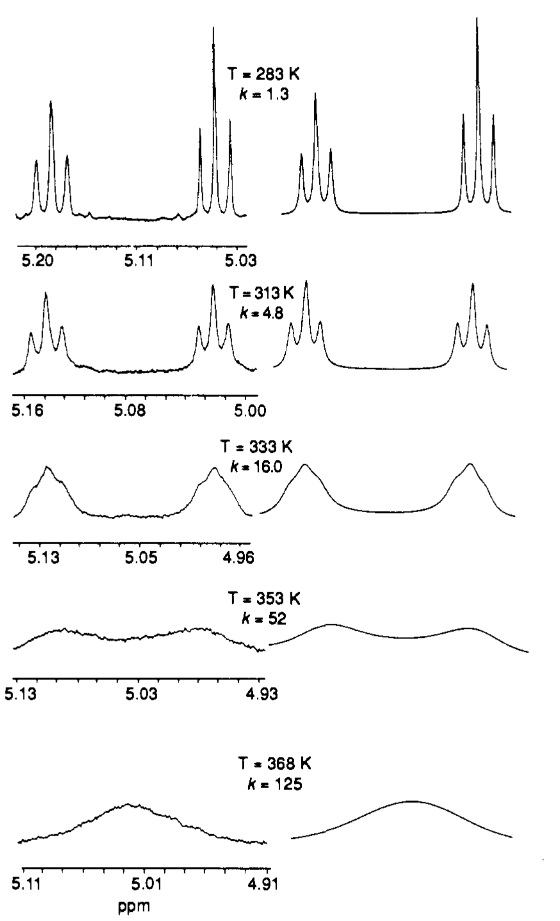


Figure 1. Representative variable-temperature 300-MHz ^1H NMR spectra of **12** in toluene-d_8 solution (left) and computer-simulated spectra (right). Temperatures are considered accurate to ±1 K.

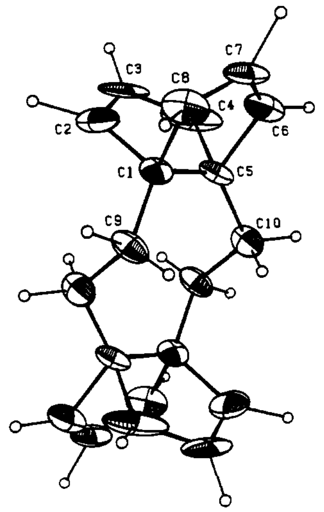


Figure 2. Crystallographic determined molecular structure of **12** as drawn with 50% probability ellipsoids. There are two half-molecules of **12** in the asymmetric unit, each of which resides around a crystallographic center of inversion.

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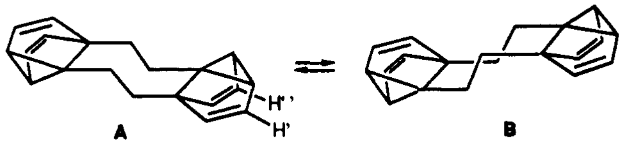
[19] See, for example: (a) Christl, M.; Kraft, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1369. (b) Tobe, Y.; Furukawa, T.; Kobiro, K.; Kakiuchi, K.; Odaira, Y. *J. Org. Chem.* **1989**, *54*, 488. (c) Kawada, K.; Gross, R. S.; Watt, D. S. *Synth. Commun.* **1989**, *19*, 777.

[20] Cheng, A. K.; Anet, F. A. L.; Mioduski, J.; Meinwald, J. *J. Am. Chem. Soc.* **1974**, *96*, 2887.

[21] (a) Askani, R.; Kalinowski, H.-O.; Weuste, B. *Org. Magn. Reson.* **1982**, *18*, 176. (b) Schneiders, C.; Müllen, K.; Braig, C.; Schuster, H.; Sauer, J. *Tetrahedron Lett.* **1984**, *25*, 749. (c) Mosaku, D.; Aydin, R.; Leber, W.; Günther, H.; Quast, H.; Martin, H.-D.; Hassenrück, K.; Miller, L. S.; Grohmann, K. *Chem. Ber.* **1989**, *122*, 925. (d) Quast, H.; Christ, J.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1985**, *118*, 1154, 1176. (e) Paquette, L. A.; Volz, W. E. *J. Am. Chem. Soc.* **1976**, *98*, 2910. (f) Iyengar, R.; Piña, R.; Grohmann, K.; Todaro, L. *J. Am. Chem. Soc.* **1988**, *110*, 2643. (g) Paquette, L. A.; James, D. R.; Birnberg, G. H. *J. Chem. Soc., Chem. Commun.* **1974**, 722. (h) Wingard, R. E., Jr.; Russell, R. K.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 7474. (i) James, D. R.; Birnberg, G. H.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 7465.

[22] Anet, F. A. L.; Anet, R.; Trova, M. P.; Paquette, L. A. *Tetrahedron Lett.* **1989**, *30*, 6469.

this basis, the conformations represented approximately by **A** and **B** should be strongly preferred, a conclusion later corroborated for **12** in the solid state. Since C_s symmetry is now clearly lacking, protons such as H′ and H″ are not magnetically equivalent as long as the rate of equilibration of **A** with **B** is sufficiently slow. The $\Delta\delta$ values vary from 0.9 to 0.17 ppm.



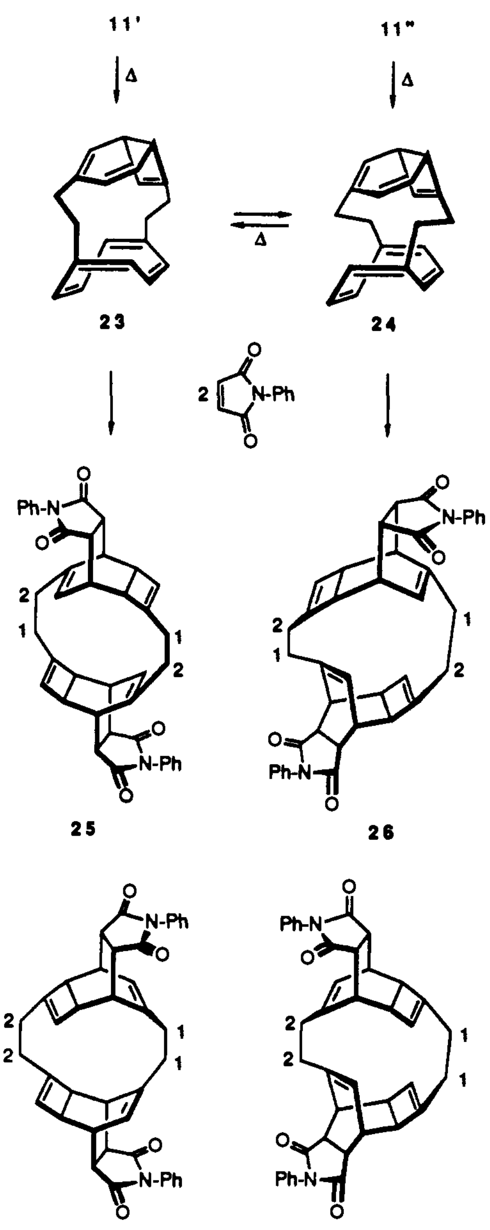
With a solvent change to toluene-d_8, it was possible to achieve ^{1}H NMR analysis at more elevated temperatures and to observe the coalescence between **A** and **B** directly (Figure 1). By this means, the equilibration has been determined to proceed with the following activation parameters: $\Delta H^{\ddagger}_{(298K)} = 11.2 \pm 0.2$ kcal/mol, $\Delta G^{\ddagger}_{(298K)} = 17.0 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger}_{(298K)} = -19.4 \pm 0.4$ eu, and $E_a = 11.8$ kcal/mol.

Single-crystal X-ray structural analysis of **12** has provided additional information about the geometry of the molecule in the solid state. As the illustration in Figure 2 reveals, the ground-state geometry is fully as expected. Otherwise, the results are quite similar to other "averaged" structures found earlier for other functionalized semibullvalenes.[24]

The conversion of **12** to **11** was accomplished thermochemically (500–510 °C) by slow introduction of an ethereal solution of **12** into a vertical quartz tube under nitrogen. The (1,5)-cyclooctatetraenophane was obtained as a colorless, crystalline solid having an elevated melting point (199–201 °C). Its ^{1}H and ^{13}C NMR spectra are temperature-invariant. The implications of this observation are detailed below.

Structural Features of the Phane. The biscyclooctatetraenophane can in principle exist as two distinctively different constitutional isomers. These are labeled as **11′** and **11″** in Scheme III and are formally distinguished by operation of bond-shift isomerization in one of the decks. Although the spectral data for **11**, most notably the remarkable unresponsiveness to changes in temperature, strongly suggest that one structural representation heavily dominates the equilibrium, no distinction between them is possible on this basis. Furthermore, the actual situation is not as simple as these lone representative formulas would imply.

Scheme IV



A more detailed profile of the actual dynamical situation is presented in Scheme IV. Where **11′** is concerned, two chiral ground-state conformations labeled as (*RS*) and (*SR*) are possible. Since these are interconverted merely by flipping the two ethano bridges, rapid passage between them is anticipated. As Moss has pointed out,[25] one less complicated way to visualize this phenomenon is to consider each cyclooctatetraene ring as a single node. As a result, the (*RS*) to (*SR*) change and its reversal are simply conformational interconversions from one form to its enantiomer *without* modification of the double bond locations.

By contrast, the conversion of **11′** to **11″**, which involves the relocation of one set of four double bonds, begets significant changes in phane conformation as reflected in Scheme IV. The inherent assumption has been made that the barriers to interconversion between the four conformers are low, such that there are not in fact six potentially isolable compounds constituted of three enantiomeric pairs. The designation of chirality adapted for these compounds follows the guidelines provided to us by Moss.[25,26]

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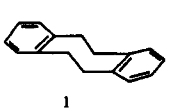
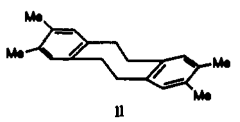
(23) Originally, the boat form was calculated to be more stable than the chair by 0.51 kcal/mol [Pauncz, R.; Ginsburg, D. *Tetrahedron* **1960**, *9*, 40]. A decade later, the chair conformation was determined to be favored by 1.79 kcal/mol [Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734]. Very low temperature NMR studies and line-shape analysis have been interpreted in terms of a twist-boat geometry, with the $\Delta G^{\ddagger}$ for TB′ → TB″ equal to 4.2 kcal/mol at −176 °C [Anet, F. A. L.; Kozerski, L. *J. Am. Chem. Soc.* **1973**, *95*, 3407]. Dibenzo derivative i is known to exist in a chair conformation in the solid state [Baker, W.; Banks, R.; Lyon, D. R.; Mann, F. G. *J. Chem. Soc.* **1945**, 27]. However, in solution the chair co-exists with


i

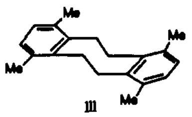
$\Delta G^{\pm}$ (chair → boat) = 10.2 kcal/mol

$\Delta G^{\pm}$ (boat′ → boat″) = 7.5 kcal/mol



ii

= 10.5 kcal.mol



iii

= 12.1 kcal/mol

the boat, with the latter form actually predominating at lower temperatures [Crossley, R.; Downing, A. P.; Nógrádi, N.; Bradode, A.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1973**, 205; see also Montecalvo, D.; St.-Jacques, M. *J. Am. Chem. Soc.* **1973**, *95*, 2023]. The energies of activation for conversion of the chair forms of ii and iii to their boat geometries have been determined [Brickwood, D. J.; Ollis, W. D.; Stephanatou, J. S.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1398].

(24) (a) Jackman, L. M.; Benesi, A.; Mayer, A.; Quast, H.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *J. Am. Chem. Soc.* **1989**, *111*, 1512 and relevant references cited therein. (b) Paquette, L. A.; Volz, W. E.; Beno, M. A.; Christoph, G. G. *J. Am. Chem. Soc.* **1975**, *97*, 256.

(25) Moss, G. P. Queen Mary and Westfield College, University of London. Private communication.

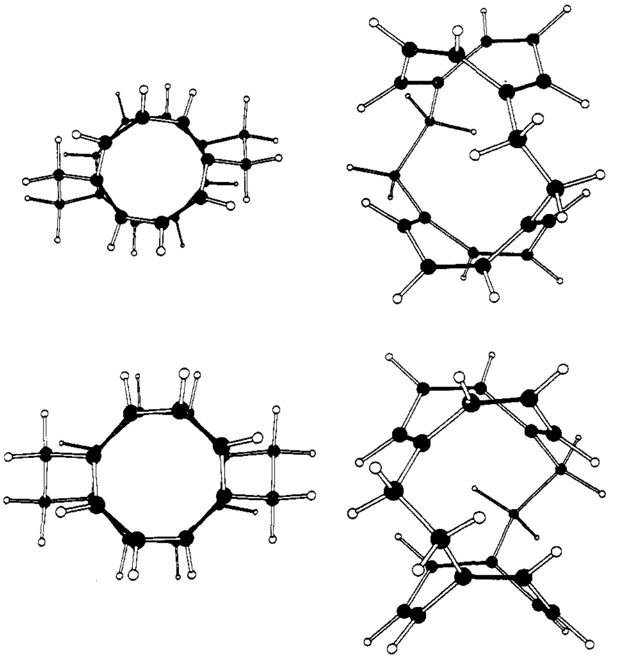


Figure 3. Perspective side and top views of the global minimum energy conformations of **11′** (top) and **11″** (bottom) as determined by molecular mechanics calculations (Chem-3D output).

Additional insight into this matter was gained by conducting a multiconformer search with the "statistical search" function of the MODEL program (version KS 2.94).[27] All 124 conformers within 5 kcal/mol of the global minimum were examined for their MM2 energy and ultimately submitted to MMX analysis for final minimization. By this means, **11″** was found to be 3.1 kcal/mol more stable than **11′**. Interestingly, the least strained structure for **11″** was found to possess a "stacked tub" arrangement of the constituent [8]annulene units, whereas the unstacked option was favored by **11′** (Figure 3).

The ultimate test of this structural question was ultimately to reside in X-ray crystallography. Single crystals of **11** were eventually grown that proved suitable for solid-state analysis. The illustrations depicted in Figure 4 were found to be in full agreement with theory on both relevant issues: the dominant bond shift isomer (viz. **11″**) and the overall molecular conformation.

Reduction Studies. Preliminarily, vacuum-line electrochemistry techniques comparable to those applied earlier to other cyclooctatetraene systems were employed at room temperature.[13c,14b,28] Tetra-*n*-butylammonium perchlorate and silver perchlorate (0.10 M) were the supporting electrolyte and reference electrode solute, respectively. Anhydrous HMPA was the solvent. Solutions were prepared at three different concentrations of **11″**, and the cyclic voltammetry of each was examined at room temperature at three different sweep rates (100–600 mV/s). Figure 5 illustrates the features of one of the more informative traces. On scanning to the point of solvent breakdown, three waves were seen at −2.65, −2.86, and −3.25 V vs Ag/Ag$^+$ (0.1 M) (−2.13, −2.34, and −2.74 V vs Ag/AgCl). They were partly irreversible, indicating the occurrence of follow-up processes.

Scheme V

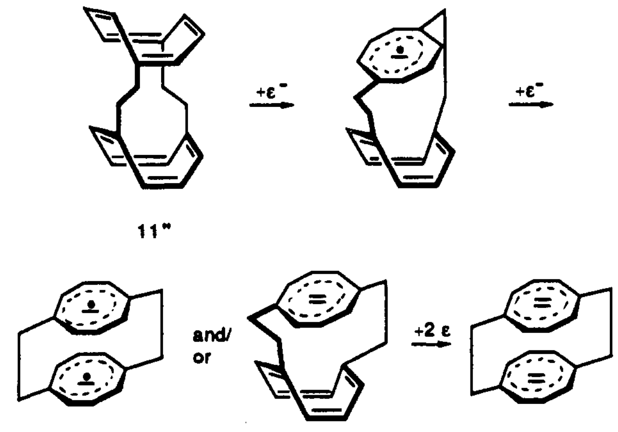


Table I. Electrochemical Parameters of the Reduction of **11″** in DMA/TBABr[a]

	X/X^-	X^-/X^{2-}	X^{2-}/X^{3-}	X^{3-}/X^{4-}
E_s° (V)	−2.43	−2.51	−2.89	−3.22[b]
k_s° (Pt)[c]	2.0×10^{-4}	2.0×10^{-4}	1.4×10^{-3}	
k_s° (Hg)[c]	8.0×10^{-4}	8.0×10^{-4}	1.2×10^{-3}	

[a] All redox potentials were determined from the average of the cathodic and anodic peak potentials and are expressed in volts vs Ag/AgCl. *T* was between 223 and 208 K. [b] The redox potential was determined by digital simulation (ref 30). [c] Heterogeneous standard rate constants (cms^{-1}) determined by the method of Nicholson [Nicholson, R. S. *Anal. Chem.* **1965**, *37*, 1351].

As these experiments showed that the reduction of **11″** occurred at considerably negative potentials, the decision was made to study its redox behavior in liquid dimethylamine (DMA). DMA is recognized to be an excellent solvent for the voltammetric generation of anions since its cathodic background limit reaches a value of −3.4 V and anions are indeed stabilized in this medium.[29] Cyclic voltammograms were measured at temperatures between 253 and 208 K (Figure 6). As can be seen, the first two quasi-reversible waves, which are almost merged, appear at potentials more positive than −2.5 V. A dianion is formed in two weakly separated one-electron redox steps with *E* potentials of −2.42 and −2.53 V. Obviously, **11″** is considerably more difficult to reduce than the parent cyclooctatetraene system. The redox potentials for mono- and dianion formation are very similar to the value observed for the first reduction step of **7**.[9] The cyclooctatetraenyl ring in the latter phane is known to exist in a tub-shaped conformation, which is difficult to flatten upon reduction because of geometrical requirements. Consequently, the redox potentials shift to more negative values. Furthermore, in contrast to the finding in COT ($\Delta E^\circ = 0.14$), the potential separation of 0.33 V between the first and second redox states of **7** is relatively large. It therefore appears in this case that stabilization of the dianionic species is less effective than in COT itself. Steric effects similar to those in **7** are at play within **11″**. The similarity of its first two redox potentials with the first redox potential of **7** reflects this common structural feature and is supportive evidence for the assumption that in **11″** both cyclooctatetraene units are reduced to their respective radical anions. The small ΔE° separation between the first two redox steps in DMA, which by virtue of a low dielectric constant favors the formation of contact ion pairs, is characteristic of a weak Coulombic through-space repulsion caused by the negative excess charge in both electrophores. In principle, one may also discuss the formation of a dianion with two electrons in one cyclooctatetraene unit instead of two radical anions in both electrophores (Scheme V). However, comparison with the data for **7** does not support this view. In this case, the second charge transfer in **11″** should occur about 0.33 V more negative than the first at a potential of −2.76 V. However, a value of −2.51 V was observed.

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(26) The use of the planar chirality priority rules for designating the chirality of these hydrocarbons is not straightforward because of problems in defining the path. Consequently, Moss has suggested to us[25] that a pilot atom p be used. The neighboring methylene group and the three atoms designated as a, b, c are then utilized to decide the direction of rotation. Since both chiral planes of each cyclooctatetraene must be identical, specification need only be made once. Hence the labels shown in Scheme IV.

(27) We thank Professor W. C. Still (Columbia University) for making this program available to us and Professor K. Steliou (University of Montreal) for updates to this software package.

(28) (a) Paquette, L. A.; Wang, T.-Z.; Luo, J.; Cottrell, C. E.; Clough, A. E.; Anderson, L. B. *J. Am. Chem. Soc.* **1990**, *112*, 239. (b) Taggart, D. L.; Peppercorn, W.; Anderson, L. B. *J. Phys. Chem.* **1984**, *88*, 2875.

(29) Meerholz, K.; Heinze, J. *J. Am. Chem. Soc.* **1989**, *111*, 2325.

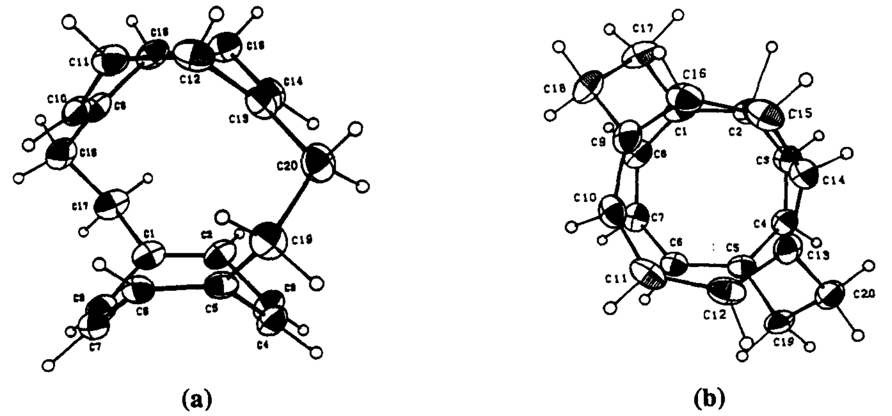


Figure 4. Side (a) and top views (b) of the crystallographically determined molecular structure of 11″ as drawn with 50% probability ellipsoids.

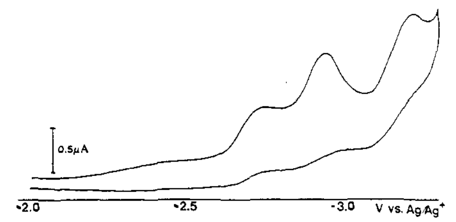


Figure 5. Cyclic voltammogram of 6.8×10^{-4} M **11** in 0.1 M TBAP/HMPA. Working electrode: Pt disk. Reference: Ag/Ag^+ (0.1 M). Scan rate: 100 mV/s.

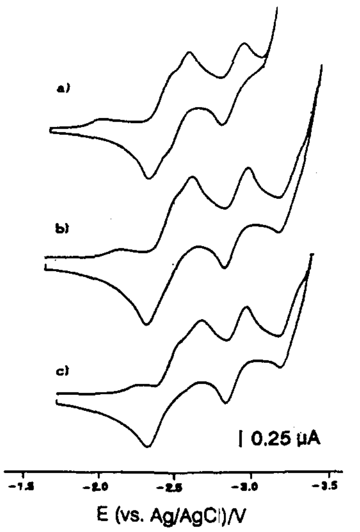
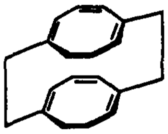


Figure 6. Cyclic voltammograms for the reduction of cyclooctatetraenophane **11**″ in DMA/TBABr, v = 100 mV s^{-1}: (a) Hg film electrode, T = 253 K; (b) Hg film electrode, T = 208 K; (c) Pt electrode, T = 208 K.

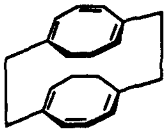
Further reduction of **11**″ to the trianion occurs at a potential that lies 0.38 V more negative than that of the monoanion/dianion couple (Table I). This value is less than that normally expected for small aromatic systems and is considered to be an indication that some planarization of the [8]annulene rings takes place concurrently with dianion formation from the neutral state despite the development of appreciable steric strain (Scheme V). Nonetheless, it agrees well with the redox potential shift ($\Delta E°$ = 0.33 V) associated with dianion formation in **7**, which is taken as further evidence for the assumption that a dianionic cyclooctatetraene subunit is formed first only at the trianion level. The last reduction step, observed uniquely at very low temperatures (Figure 6c), suggests that a tetraanionic species is ultimately formed with two excess charges in both cyclooctatetraenyl subunits. Although the wave lies in the rise of the background current and therefore is only partly visible, digital simulation clearly indicates formation of the tetraanion.[30] The separation between the third and fourth redox steps ($\Delta E°$ = 0.33 V) is due to the fact that strong Coulombic repulsions between the closely spaced cyclooctatetraenyl dianion decks now make their presence felt. The analogous repulsive interactions in bicyclooctatetraenyl are significantly weaker ($\Delta E°$ = 0.24 V),[31] although in that case conjugative interactions might enhance the repulsion.

The structural changes that occur during reduction are also reflected in the heterogeneous kinetics. The rate constants for the first two redox steps at a platinum electrode are rather small, indicating sluggish kinetics to be at hand. This stems from internal structural reorganization processes associated with some flattening of the cyclooctatetraenyl rings that heighten the activation energy. When a mercury surface was utilized instead as the electrode, the rate constant values were seen to be slightly higher, since no passivated metal surface now existed to initiate filming processes. The fact that the heterogeneous kinetics are slow for the first two redox steps is additional support for the view that both cyclooctatetraenyl units are reduced during these redox processes, forming a diradical species. The rate values of the third electron transfer are significantly higher than those associated with mono- and dianion formation. For this reason, we assume that, if further planarization of the [8]annulene rings is occurring during these events, it is quite limited.

Preparative-scale electrochemical reduction of **11** was also carried out in anhydrous HMPA solutions containing TBAP under the control of a potentiostat operating at −2.86 V vs Ag/Ag^+ (0.1 M). After 12 h, water was added and the product mixture was extracted into petroleum ether. The two major products were identified by GC–MS as possessing m/z 264, corresponding to the addition of four protons. No doubly protonated product having a mass of 262 was detected. Chromatographic isolation provided an inseparable 1:1 mixture of **21** and **22**, which were identified as the isomeric cyclooctatrienophanes shown by means of ^1H NMR decoupling experiments performed at 300 MHz.



21



22

These results suggest either that disproportionation of the COT phane dianion is occurring under these conditions or that the dianion is abstracting protons from solvent, electrolyte, or adventitious moisture in the solvent such that further reduction is possible at the operating potential indicated.

Cycloaddition Behavior. Should **11** undergo Diels–Alder cycloaddition in the same manner as the parent cyclooctatetraene, prior valence isomerization to **23** and/or **24** must materialize prior to initial capture of the dienophile (Scheme VI). Although these

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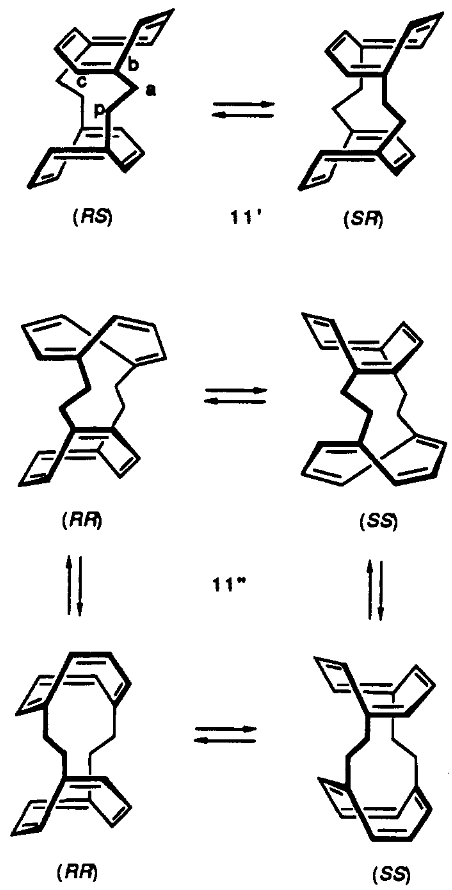
(30) Heinze, J.; Störzbach, M.; Mortensen, J. *J. Electroanal. Chem.* **1984**, *165*, 61.

(31) Taggart, D. L. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1975.

Scheme VI



tautomers arise from electrocyclization within **11′** and **11″**, respectively, the thermal activation needed to accomplish these structural changes is certain to exceed the temperature at which bond shifting in the other deck will materialize and lead to their interconversion. Consequently, tracking the course of these events at the mechanistic level was not considered feasible.

The actual state of affairs is somewhat more complicated because we have not found it possible to isolate monoaddition products. Thus, heating equimolar amounts of **11** and *N*-phenylmaleimide in xylene solution at 120 °C required 17 h to achieve 17% conversion to a 94:6 mixture of two bis-adducts. Of the four possible candidates for major product, **25** and **26** were quickly ruled out on the basis of COSY experiments that showed vicinal coupling between the protons on C(1) and C(2) to be absent. As a consequence of their symmetry characteristics, the lack of spin interaction between the two four-proton multiplets centered at δ 2,2 and 1.0 (in $CDCl_3$) indicates the adjacent methylene protons to be magnetically equivalent.

While this is so in **27** and **28**, their distinction is not as straightforward. When these molecules are maintained in their more stable conformations, the cyclobutene (δ 5.54, s) and cyclohexene protons (δ 5.50, d, J = 6.6 Hz) are seen to be more proximal in **28** than in **27**. While double irradiation of these signals in the major isomer did give rise to some enhancement of the respective integrals, the minor adduct exhibited a still larger NOE effect. Although this evidence is far from conclusive, the available evidence points to **27** as the major adduct and to **28** as the minor. Unfortunately, the crystals of the dominant bis(imide) could not be grown into a form suitable for X-ray crystallographic analysis.

Conclusions

A synthesis of (1,5)cyclooctatetraenophane **11** is outlined that is expected to hold general applicability for the construction of structurally allied doubly-decked [8]annulenes. Modifications allowing for the control of tether length, chemical constitution, and location of the interconnective bridges should be possible. While the conformational dynamics of **11** are already complex, the insertion of longer, more flexible bridges is certain to be accompanied by increased degrees of freedom.

Electrochemical reduction studies have indicated that, although the tetraanion is quite difficult to generate, homolytic cleavage of one of the ethano bridges does not occur to alleviate the intense Coulombic forces at work.

Finally, the steric crowding that exists between the decks of **11** and the other constraints present in this cyclophane do not combine to inhibit valence isomerization to bicyclo[4.2.0]octatriene subunits. Our inability to obtain monoadducts suggests that the first electrocyclization may be more difficult to accomplish than the second, but this working assumption has not yet been proven.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Bruker AC-300 instrument. Mass spectra were recorded on a Kratos MS-30 instrument at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The chromatographic separations were carried out either under flash conditions on Fluka silica gel H or gravimetrically on Woelm silica gel 63–200. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

Osmylation–Acetalization of 15. A solution of **15**[17] (500 mg, 2.29 mmol) in THF (2 mL) was added to a solution of *N*-methylmorpholine *N*-oxide (400 mg, 3.44 mmol) and osmium tetraoxide (5.8 mg, 0.023 mmol) in THF (5 mL) and aqueous *tert*-butyl alcohol (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, and freed of solvent in vacuo. The residue was taken up in ethyl acetate (30 mL) and washed with 10% HCl (2 × 10 mL). The acidic aqueous layers were back-extracted with chloroform (4 × 10 mL). The combined organic phases were dried, filtered, and evaporated to leave a white solid. The acidic aqueous phase was continuously extracted with ethyl acetate for 10 days, and the additional diol so recovered was dissolved in acetone (10 mL) containing *p*-toluenesulfonic acid (20 mg). This solution was stirred overnight and evaporated. The residue was taken up in chloroform (40 mL) and washed sequentially with dilute aqueous Na_2CO_3 solution (2 × 20 mL), water, and brine prior to drying and evaporation. The solid so obtained was recrystallized from ether to give **17** as colorless crystals: mp 125–126 °C (555 mg, 83%); IR (KBr, cm^{-1}) 1725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (m, 2 H), 2.69 (d, J = 19.9 Hz, 2 H), 2.41 (s, 4 H), 2.35 (d, J = 19.9 Hz, 2 H), 2.10–1.80 (m, 4 H), 1.80–1.60 (m, 2 H), 1.52 (ddd, J = 15.1, 7.4, 3.0 Hz, 2 H), 1.43 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 215.8, 215.0, 108.0, 77.9 (2C), 53.8 (2C), 50.7 (2C), 48.5 (2C), 31.1 (2C), 28.5, 25.8, 25.9 (2C); MS m/z (M^+) calcd 292.1674, obsd 292.1653. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.82; H, 8.28. Found: C, 69.82; H, 8.26.

Hydride Reduction of 17. A solution of **17** (5.00 g, 17.1 mmol) in THF (200 mL) was added dropwise over 30 min to a slurry of lithium aluminum hydride in THF (300 mL) at 0 °C. The mixture was stirred at room temperature for 30 min, cooled to 0 °C, and treated cautiously with saturated sodium potassium tartrate solution (5 mL). The organic solution was decanted from the precipitated solid, which was dissolved in water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic solutions were washed with brine, dried, and evaporated to leave a clear oil, purification of which by column chromatography (elution with 10% ethanol in petroleum ether) gave 4.88 g (96%) of crystalline diol isomers. One of the diastereomers was separable by further chromatography: mp 142–143 °C; IR ($CHCl_3$, cm^{-1}) 3250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (br s, 2 H), 4.38 (t, J = 6.4 Hz, 1 H), 4.21–4.14 (m, 3 H), 2.27 (dd, J = 15.0, 6.7 Hz, 2 H), 2.09 (d, J = 14.0 Hz, 2 H), 1.95 (d, J = 14.0 Hz, 2 H), 1.83 (dd, J = 15.0, 6.2 Hz, 2 H), 1.80–1.44 (m, 6 H), 1.40 (s, 3 H), 1.31 (s, 3 H), 1.20–1.00 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 107.2, 78.8 (2C), 73.4, 72.4, 54.7 (2C), 54.6 (2C), 49.0 (2C), 33.3 (2C), 28.1, 25.4 (3C); MS m/z ($M^+ - CH_3$) calcd 281.1752, obsd 281.1768. Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.87; H, 9.53. Found: C, 68.83; H, 9.47.

Chugaev Elimination. A solution of the above diol (340 mg, 1.15 mmol) in THF (15 mL) was added dropwise to a mixture of sodium hydride (220 mg of 97%, 9.17 mmol) in dry carbon disulfide (20 mL). This mixture was refluxed for 45 min, cooled to room temperature, and treated with methyl iodide (4.90 g, 34.5 mmol). After 20 min of stirring, the mixture was refluxed for 30 min, the heat was removed, and stirring was maintained for an additional 4 h. Water (2 mL) was cautiously introduced, followed by additional water (20 mL) and ether extraction (4 × 20 mL). The combined organic phases were washed with water and brine and then dried and evaporated to leave the bis(xanthate) as a yellow oil.

This oil was deposited in a flask equipped with an air-cooled condenser. The flask was immersed in a preheated (200–210 °C) oil bath for 30 min and allowed to cool. The contents were subjected to chromatography (elution with 10% ethyl acetate in petroleum ether). The yellow oil so obtained was crystallized from methanol to give **18** as clear needles (215 mg, 72%): mp 94–96 °C; IR (KBr, cm^{-1}) 1620, 1370, 1360, 1235, 1215, 1145, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70–5.20 (m, 4 H), 4.30–4.10 (m, 2 H), 2.80–1.10 (series of m, 18 H) (the 4 methyl singlets appear at 1.40, 1.38, 1.30, and 1.29); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 143.0, 138.9, 138.4, 136.5, 130.3, 128.1, 125.9, 125.1, 107.3, 107.1, 81.6, 80.5, 78.1, 77.1, 66.0, 60.3, 59.4, 52.9, 49.1, 46.7, 44.9, 41.1, 31.4, 30.1, 29.5, 28.8, 28.4, 28.2, 26.7, 25.9, 25.6, 25.5, 23.6, 23.5; MS *m/z* (M^+) calcd 260.1776, obsd 260.1789. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.41; H, 9.30. Found: C, 78.43; H, 9.29.

Hydrolysis of 18. A solution of **18** (60 mg, 0.23 mmol) in 90% methanol (20 mL) containing *p*-toluenesulfonic acid (10 mg) was refluxed for 16 h and evaporated. Chromatographic purification (elution with 50% ethyl acetate in petroleum ether) gave 41.2 mg (81%) of the diol mixture, the recrystallization of which from ether afforded colorless crystalline needles: mp 98–99 °C; IR (KBr, cm^{-1}) 3330, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80–5.10 (m, 4 H), 4.00–3.70 (m, 2 H), 2.80–1.10 (series of m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 142.7, 140.2, 136.9, 136.7, 128.8, 127.5, 127.4, 125.5, 75.6, 73.5, 73.2, 71.1, 66.6, 59.4, 53.5, 48.3, 46.1, 43.2, 32.1, 30.5, 28.8, 27.7, 27.1 (2C), 26.8, 26.7; MS *m/z* (M^+) calcd 229.1463, obsd 220.1473. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.16. Found: C, 76.13; H, 9.15.

Diketone 14. To a cold (−78 °C), magnetically stirred solution of oxalyl chloride (1.30 g, 10.27 mmol) in dry CH_2Cl_2 (35 mL) was added dry DMSO (960 mg, 12.33 mmol). Five minutes later, a solution of the above diol (1.00 g, 4.55 mmol) in dry CH_2Cl_2 (20 mL) was introduced dropwise. The mixture was stirred at −78 °C for 1 h, at which point triethylamine (2.74 g, 27.2 mmol) was added and warming to room temperature was allowed. The solvent was evaporated, and the residue was taken up in ether and filtered. The filtrate was freed of solvent to leave a pale green oil that was purified by chromatography (elution with 10% ethyl acetate in petroleum ether) to give 680 mg (69%) of **14** as a colorless crystalline solid: mp 86–87 °C (from ether); IR (neat, cm^{-1}) 1730, 1710; ^1H NMR (300 MHz, $CDCl_3$, one isomer) δ 5.68 (dt, J = 5.8, 2.4 Hz, 2 H), 5.47 (dt, J = 16.8, 2.2 Hz, 2 H), 2.68–2.57 (m, 4 H), 2.38 (dt, J = 16.8, 2.2 Hz, 2 H), 2.07 (dt, J = 16.6, 2.3 Hz, 2 H), 1.98–1.85 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) (isomer A) 209.3, 208.3, 135.1, 128.8, 64.9, 54.2, 45.2, 35.9, 35.5, 29.3, 27.4, (isomer B) 209.1, 139.8, 127.0, 60.1, 41.8, 36.1, 28.5; MS *m/z* (M^+) calcd 216.1150, obsd 216.1164. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.59; H, 7.49.

Diketone 19. To a solution of **14** (620 mg, 2.87 mmol) in methanol (6 mL) were added in turn pH 5.6 buffer (10 mL), dimethyl 3-ketoglutarate (1.00 g, 5.74 mmol), more methanol (3 mL) to complete the dissolution, and a few more drops of buffer to render the solution turbid. The mixture was stirred vigorously for 4 days, and the resulting precipitate was separated by filtration, washed with methanol, and dried.

The white solid so obtained (630 mg, 91%) was refluxed with 10% HCl (36 mL) and glacial acetic acid (18 mL) for 5 h and then allowed to cool. Following the addition of chloroform (20 mL), saturated Na_2CO_3 solution was introduced slowly until pH 8 was attained. The aqueous phase was extracted with chloroform (4 × 20 mL), and the combined organic solutions were washed with water and brine prior to drying. The solvent was evaporated, and the residue was purified by chromatography (elution with 30% ethyl acetate in petroleum ether) to give 300 mg (85%) of **19** as a colorless solid: mp 203–205 °C; IR (KBr, cm^{-1}) 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70–5.20 (series of m, 4 H), 2.80–1.40 (series of m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 216.2, 141.1, 128.7, 126.8, 66.1, 53.1, 49.2, 48.6, 48.3, 48.1, 42.0, 31.4, 30.8, 30.3, 29.9, 29.6, 28.7; MS *m/z* (M^+) calcd 296.1776, obsd 296.1777. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.03; H, 8.17. Found: C, 80.84; H, 8.10.

Hydride Reduction of 19. To a cold (0 °C), magnetically stirred slurry of $LiAlH_4$ (710 mg, 18.7 mmol) in dry THF (100 mL) was added a solution of **19** (2.64 g, 8.9 mmol) in THF (40 mL) during 20 min. The mixture was stirred at room temperature for 2 h, returned to 0 °C, and quenched by careful addition of a dilute sodium potassium tartrate solution. After decantation, the residual solid was washed with THF, and the combined organic solutions were dried and evaporated to leave 2.58 g (96%) of a mixture of epimeric alcohols: IR (KBr, cm^{-1}) 3320; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70–5.20 (series of m, 4 H), 4.00–3.70 (br m, 2 H), 2.70–1.20 (series of m, 20 H); MS *m/z* (M^+) calcd 300.2089, obsd 300.2078.

Tetraene 20. To a mixture of NaH (74 mg of 97%, 3.0 mmol) in dry THF was added dropwise a solution of the above diol (90 mg, 0.30 mmol) in a 1:1 mixture of CS_2 and THF (20 mL). The reaction mixture was refluxed for 1 h, cooled to room temperature, and treated with methyl iodide (852 mg, 6.0 mmol). After 1 h of reflux and workup in the manner described earlier, a dark orange bis(xanthate) was isolated and heated at 210 °C for 45 min. Following chromatography (elution with petroleum ether) and crystallization from methanol, **20** was obtained as a colorless solid: mp 111–112 °C (48 mg, 60%); IR (KBr, cm^{-1}) 1620, 1465, 1350, 1335, 1285, 960, 800, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90–5.10 (series of m, 8 H), 2.90–1.90 (series of m, 8 H), 1.90–1.10 (br m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 143.8, 142.2, 139.3, 136.9, 136.3, 127.9, 125.5, 125.0, 60.2, 59.9, 58.7, 52.8, 45.0, 42.2, 40.3, 31.2, 30.9, 29.8, 29.1, 27.8; MS *m/z* (M^+) calcd 264.1878, obsd 264.1905. Anal. Calcd for $C_{20}H_{24}$: C, 90.84; H, 9.16. Found: C, 90.66; H, 9.23.

Bis(semibullvalene) 12. A mixture of **20** (300 mg, 1.14 mmol), *N*-bromosuccinimide (817 mg, 4.59 mmol), and AIBN (10 mg) in carbon tetrachloride (15 mL) was refluxed for 20 min, cooled, and filtered. The succinimide was washed with CCl_4, and the combined filtrates were evaporated to leave a residue that was taken up in dry, nitrogen-saturated DMF (20 mL) and added dropwise to a solution of $Ni(CO)_4$ (2.4 mL) in the same solvent (120 mL) at 50 °C over 12.5 h. After the reaction mixture stood overnight, the excess $Ni(CO)_4$ was removed in vacuo and the solution was poured into water (250 mL) prior to extraction with pentane (5 × 100 mL). The combined pentane extracts were washed with water and brine, dried, and evaporated to leave a yellow solid. Chromatography of this material (elution with petroleum ether) gave 115 mg (39%) of **12** as a colorless crystalline solid: mp 192–193 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (t, J = 3.8 Hz, 2 H), 4.99 (t, J = 3.8 Hz, 2 H), 4.18 (t, J = 3.8 Hz, 4 H), 4.09 (t, J = 3.8 Hz, 4 H), 1.60–1.40 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 120.4, 118.6, 94.1, 91.6, 65.2, 26.8; MS *m/z* (M^+) calcd 260.1565, obsd 260.1572. Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 91.83; H, 7.75.

[2_2](1,5)Cyclooctatetraenophane (11). Bis(semibullvalene) **12** (71.8 mg, 0.28 mmol) in ether (10 mL) was introduced dropwise under nitrogen at a rate of 0.2 mL/min (syringe pump) into a vertical pyrolysis oven packed with quartz chips and heated to 500 °C. The pyrolysate was collected in a U-tube at −78 °C. The cooled column was rinsed with ether. The ethereal solution was carefully evaporated, and the residue was chromatographed (elution with petroleum ether) to return 8 mg (10%) of unrearranged **12** and to provide 23 mg (32%) of **11** as a colorless crystalline solid: mp 199–201 °C (from petroleum ether); IR ($CHCl_3$, cm^{-1}) 1645, 1430, 1350, 1260, 1195, 1100, 825; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dd, J = 11.3, 3.4 Hz, 4 H), 5.60 (d, J = 11.3 Hz, 4 H), 5.43 (d, J = 3.4 Hz, 4 H), 2.13 (s, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 140.2, 133.2, 132.2, 129.7, 36.9; MS *m/z* (M^+) calcd 260.1565, obsd 260.1561. Anal. Calcd for $C_{20}H_{20}$: C, 92.25; H, 7.75. Found: C, 92.26; H, 7.74.

Electrochemistry of 11. A. In HMPA. Cyclic voltammograms of **11** in HMPA were performed under oxygen-free conditions using previously-employed vacuum-line techniques.[31] The working electrode was a Pt disk (0.02 cm^2). The auxiliary electrode was a Pt wire. An Ag wire in a 0.1 M $AgClO_4$/HMPA solution acted as the reference. The supporting electrolyte was 0.1 M TBAP. Potential control was accomplished with a PAR Model 173 potentiostat/galvanostat and a Krohn-Hite Model 5200 function generator. Voltammograms were recorded using a Hewlett-Packard 2D-2M X-Y recorder.

Silver perchlorate was used as received. Tetrabutylammonium perchlorate (TBAP) was dried overnight under vacuum prior to use. Hexamethylphosphoramide (HMPA) was dried by sodium addition and vacuum distillation.

B. In Me_2NH. All voltammetric measurements performed on dimethylamine solutions were carried out with a PAR Model 137 potentiostat/galvanostat and a PAR Model 175 universal programmer. Cyclic voltammograms were recorded with an HP Model 7004B X-Y recorder. A three-electrode configuration was employed throughout. The working electrode was a Pt disk sealed in soft glass (diameter ϕ 1.00 mm). The reference electrode was an Ag wire, on which AgCl had been deposited electrolytically, immersed in the electrolyte solution. Potentials were calibrated against the formal potential of the $[Cp_2Co]^+/[Cp_2Co]$ couple (−0.92 V vs Ag/AgCl). All manipulations were carried out under an argon atmosphere. The electrochemical cell, of special construction, was equipped with an internally integrated drying compartment. Details are described elsewhere.[32,33] Dimethylamine (DMA) was dried by refluxing over highly activated alumina.

Diels–Alder Addition to 11. A solution of **11** (55 mg, 0.21 mmol) and *N*-phenylmaleimide (90 mg, 0.53 mmol) in xylene (20 mL) was heated

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(32) Kiesele, H. *Anal. Chem.* **1981**, *53*, 1952.

(33) Hinkelmann, K.; Heinze, J.; Schacht, H.-T.; Field, J.; Vahrenkamp, H. *J. Am. Chem. Soc.* **1989**, *111*, 5078.

at 120 °C for 17 h. On cooling, the adduct precipitated and was removed by filtration (22 mg, 17%, or 27% based on recovered **11**): white solid, mp > 250 °C, consisting of a 94:6 mixture of isomers (^{1}H NMR analysis); IR (CCl$_4$, cm^{-1}) 1710; ^{1}H NMR (300 MHz, CDCl$_3$) (major isomer) δ 7.46–7.06 (m, 10 H), 5.54 (s, 2 H), 5.50 (d, J = 6.6 Hz, 2 H), 3.26 (dt, J = 3.0, 6.6 Hz, 2 H), 3.05 (br s, 2 H), 2.99 (dd, J = 3.1, 8.0 Hz, 2 H), 2.90 (dd, J = 2.8, 8.0 Hz, 2 H), 2.78 (s, 4 H), 2.72–2.67 (m, 4 H), 2.15–2.03 (m, 4 H); ^{13}C NMR (63 MHz, CDCl$_3$, ppm) 178.2, 177.7, 150.9, 139.6, 132.0, 129.2, 128.6, 128.2, 126.5, 119.0, 44.8, 44.2, 41.4, 39.6, 36.3, 30.0, 24.4; MS m/z (M$^+$) calcd 606.2519, obsd 606.2514.

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Supplementary Material Available: Figure of the second molecule of **12** and crystallographic experimental procedures and tables of X-ray crystal data, bond lengths and angles, final fractional coordinates, thermal parameters, and least-squares planes for **11** and **12**, as well as final computed coordinates for **11′** and **11″** (16 pages). Ordering information is given on any current masthead page.

Thiolation of Uridine Carbon-2 Restricts the Motional Dynamics of the Transfer RNA Wobble Position Nucleoside

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Abstract: Thiolation of transfer RNA wobble position uridines produces a preferred conformation of the nucleoside in solution at ambient temperature that is of biological significance to codon recognition [Sierzputowska-Gracz, H.; Sochacka, E.; Malkiewicz, A.; Kuo, K.; Gehrke, C.; Agris, P. F. *J. Am. Chem. Soc.* **1987**, *109*, 7171–7177]. We investigated and compared, by proton nuclear magnetic resonance (NMR) spectroscopy, the thermodynamic stability of the conformations of 2-thiouridine and five biologically important 5-position derivatives and the six analogous uridines. Under physiological conditions, there were 4.8 times larger values of enthalpy and an average change of 1 kcal/mol, ΔG, for the C(2′) to C(3′) endo transitions of the 2-thiouridines, found to favor the C(3′) endo conformation, than for the respective non-thiolated uridines, found preferentially in the C(2′) endo conformation. The effect of an adjacent nucleoside on the structures and dynamics of 2-thiouridine and uridine was studied by analyzing the dinucleoside s^{2}UpU. Within the dinucleoside the individual nucleosides neither differed in structure nor dynamics from their respective mononucleosides. Therefore, the 2-position thiolation, and not the 5-position modification, produced a significantly more stable, motionally more restricted, C(3′) endo, gauche plus, anti conformer. This thermodynamically preferred structure may be best suited for anticodon base stacking and loop and stem stability. The result in tRNA is a modified-wobble selection of adenine as the only suitable third base of the codon.

Uridines (U) in the first or wobble position of transfer RNA anticodons are many times found to be naturally thiolated at carbon-2 and otherwise modified at carbon-5.[1] Thus, codon recognition by the tRNAs wobble position modified uridine may be dependent on the nucleoside's conformation as conferred by its 2- and/or 5-position modifications. We found that at ambient temperature thiolation of uridine produced a C(3′) endo, gauche plus, anti structure irrespective of the 5-position modification and postulated that this conformation is biologically significant.[2] Mutations producing a dramatic decrease in uridine thiolation and the loss of 2-thio-5-[(methylcarboxy)methyl]uridine had been found to inactivate the UGA and UAA suppressor serine tRNAs of *Schizosaccharomyces pombe* in vivo.[3,4] However, the biologically important conformation of modified uridine in tRNA may be that which is most thermodynamically stable. Therefore, we compared the enthalpy and energy requirements (ΔG) for ribose C(2′) endo to C(3′) endo transitions of 2-thiouridine (s^{2}U) and five differently modified 5-position s^{2}Us to that of the analogous U's (Figure 1). In addition, we analyzed the conformation and thermodynamic stability of s^{2}U and U in the dinucleoside s^{2}UpU (Figure 1). Here we report that the thio group imparted to the nucleoside, alone or in the dinucleoside, a thermodynamically stable C(3′) endo, gauche plus, anti conformation.

Experimental Section

Synthesis of Nucleosides and Dinucleoside. All nucleosides were chemically synthesized with the exception of uridine (U) which was purchased from Sigma Chemical (St. Louis). The chemical syntheses and purification of the modified nucleosides (compounds II–XII, Figure 1) were reported previously: II, 2-thiouridine, s^{2}U; III, 5-[(methylamino)methyl]uridine, mnm^{5}U; IV, 2-thio-5-[(methylamino)methyl]uridine, s^{2}mnm^{5}U; V, 5-methoxyuridine, mo^{5}U; VI, 2-thio-5-methoxyuridine, s^{2}mo^{5}U; VII, uridine-5-oxyacetic acid methyl ester, mcmo^{5}U;

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(1) Bjork, G. R.; Ericson, J. U.; Gustafsson, C. E. D.; Hagervall, Y. H.; Wilkstrom, P. M. *Ann. Rev. Biochem.* **1987**, *56*, 263–287.

(2) Sierzputowska-Gracz, H.; Sochacka, E.; Malkiewicz, A.; Kuo, K.; Gehrke, C.; Agris, P. F. *J. Am. Chem. Soc.* **1987** *109*, 7171–7177.

(3) Heyer, W. D.; Thuriaux, P.; Kohli, J.; Ebert, P.; Kersten, H.; Gehrke, C.; Kuo, K. C.; Agris, P. J. *J. Biol. Chem.* **1984**, *259*, 2856–2862.

(4) Grossenbacher, A. M.; Stadelmann, B.; Heyer, W. D.; Thuriaux, P.; Kohli, J.; Smith, C.; Agris, P. F.; Kuo, K. C.; Gehrke, C. *J. Biol. Chem.* **1986**, *261*, 16351–16355.