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Synthesis of Novel Benzenoid Molecules by Low-Valent-Titanium Deoxygenation

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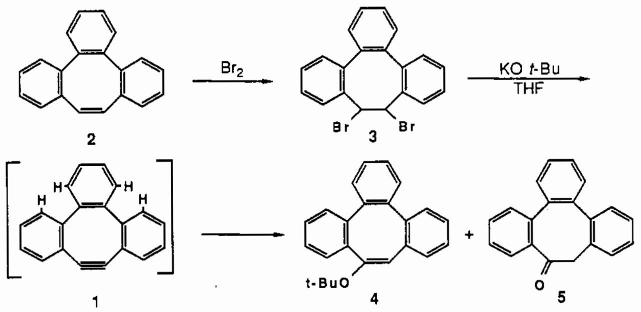
The attempts to explain unequivocally the concept of "aromaticity" have furnished an active area for the correlation of theory and experiment in organic chemistry.[1] Our research efforts in this domain have been directed toward the studies of coplanar benzo-fused dehydro[8]annulenes.[2] During our quest for the presumably planar 13,14-didehydrotribenzo[*a*,*c*,*e*]cyclooctene (**1**) (Scheme I), we were halted at the final step when **3** was subjected to dehydrobromination with KO-*t*-Bu, the usual base for such systems.[3] Instead of the desired **1**, a secondary product **4** together with its hydrolysis remnant **5** was isolated after careful hydrolysis and chromatographic separation.[3] The peri H–H repulsion of the expected coplanar **1** was thought to be responsible for its instability, and not surprisingly, **1** succumbed to nucleophilic attack by the *tert*-butoxide ion.

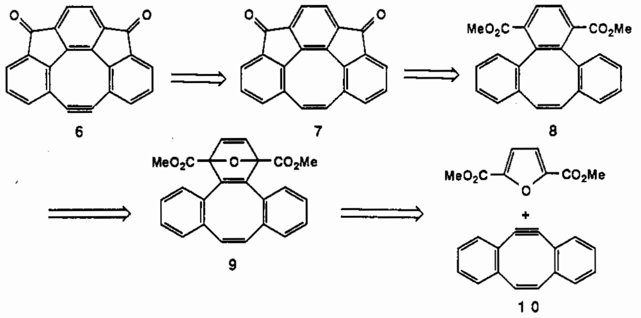
In a continuation of the study of **1**, we reasoned that the structurally related **6**, having the detrimental peri hydrogens erased, might sustain some degree of stability. Our retrosynthesis (Scheme II) of **6** required the polycyclic **7** and thereupon ester **8** as the key intermediates. Diketone **7** itself was expected to be an interesting molecule since the constraint imposed by the keto bridges would render the eight-membered ring nearly coplanar and thus to a certain degree paratropic.

A literature survey revealed that even the synthesis of the parent tribenzo[*a*,*c*,*e*]cyclooctene (**2**) was not a trivial maneuver. Although **2** has been known for almost 45 years,[4] its practical preparations were not published until 1980.[3,5] However, encouraged by the general applicability of the construction of aromatic systems[6,7] via 1,4-endoxides (e.g., **9**) followed by oxygen extrusion, we set forth to undertake the preparation of **8** from **9**, which in principle could be obtained from the Diels–Alder reaction of dimethyl furan-2,5-dicarboxylate and the strained alkyne **10** previously reported by us.[8] A double intramolecular Friedel–Crafts acylation[9] of **8** was expected to deliver our desired precursor **7**. It was this specific need to procure **7** that eventually led to the development of a general synthetic methodology for the preparation of novel benzenoid systems.

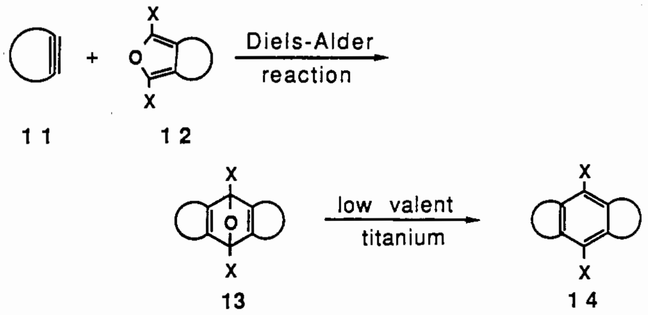
Scheme I



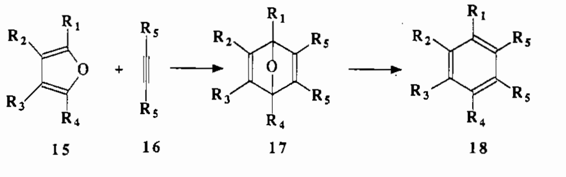
Scheme II



Scheme III



Scheme IV



Described in this Account is a highly flexible strategy that has led to widespread applications for the synthesis of some novel benzenoid molecules (vide infra). The pivotal steps of our method involve the formation of an endoxide and its subsequent deoxygenation by the low-valent-titanium reagent[10] generated by in situ re-

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The biography of the author (also known as Nai Zheng Huang) has appeared in a previous issue (*Acc. Chem. Res.* **1982**, *15*, 96–102). After working for two years in the Shanghai Institute of Organic Chemistry, Henry Wong returned to Hong Kong in 1982 to take up teaching at the Hong Kong Polytechnic. A year later, he rejoined the Chinese University of Hong Kong, his alma mater, where he is now Senior Lecturer in Chemistry. Concurrently, he is also Visiting Professor of Lanzhou University, China. His research interests include the synthesis and studies of theoretically interesting molecules as well as the identification and synthesis of biologically active compounds from Chinese herbs.

(1) Garratt, P. J. *Aromaticity*; Wiley-Interscience: New York, 1986. Lloyd, D. *Non-benzenoid Conjugated Carbocyclic Compounds*; Elsevier: Amsterdam, 1984.

(2) For a review, see: Huang, N. Z.; Sondheimer, F. *Acc. Chem. Res.* **1982**, *15*, 96–102.

(3) Wong, H. N. C. Ph. D. Thesis, University College London, 1973. Chan, T.-L.; Huang, N. Z.; Sondheimer, F. *Tetrahedron* **1983**, *39*, 427–432. See also: Gugel, H.; Meier, H. *Chem. Ber.* **1980**, *113*, 1431–1443.

(4) Shuttleworth, R. G.; Rapson, W. S.; Stewart, E. T. *J. Chem. Soc.* **1944**, 71–73.

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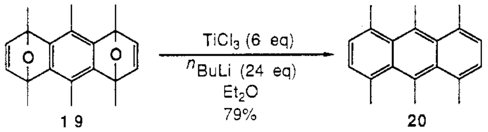
Table I
Cycloaddition of 15 and 16 and Deoxygenation of 17 with the Low-Valent-Titanium Reagent

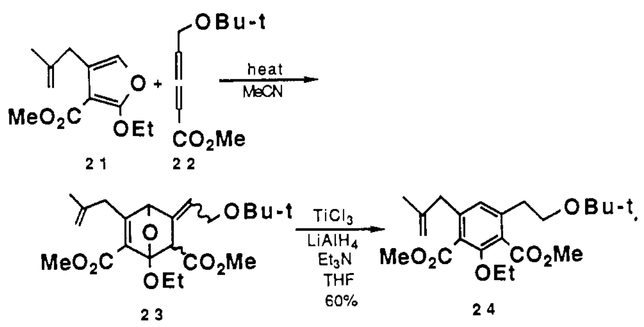
	R_1	R_2	R_3	R_4	R_5	yield, % 17	yield, % 18	ref
a	H	H	H	H	CO_2Me	47	64	14
b	Me	H	H	H	CO_2Me	71	77	14
c	Me	H	H	Me	CO_2Me	81	54	14
d	H	CO_2Me	CO_2Me	H	CO_2Me	44	59	16
e	Me	CO_2Me	CO_2Me	H	CO_2Me	80	50	16
f	Me	CO_2Me	CO_2Me	Me	CO_2Me	46	30	16
g	H	H	H	H	CF_3	88	60	16
h	Me	H	H	H	CF_3	83	73	16
i	Me	H	H	Me	CF_3	51		16

Scheme V

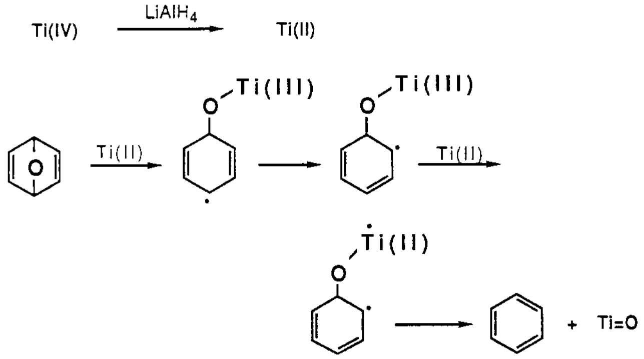


duction of titanium(IV) chloride with $LiAlH_4$ in Et_3N and tetrahydrofuran (THF). In its general form, this overall strategy can be represented as in Scheme III. By proper regulation of the structures of acetylene **11** and furan **12**, a variety of endoxides **13** and thereby benzenoids **14** can be obtained.

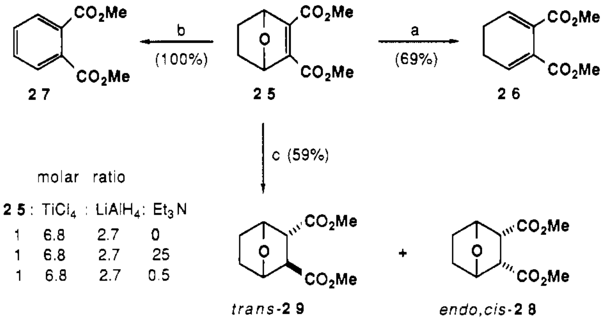
Scheme VI



Scheme VII



Scheme VIII



Deoxygenation of 1,4-Endoxides and the Synthesis of Substituted Benzenes

Since Diels–Alder cycloaddition between activated alkynes and furans had been well-documented,[11] our early efforts were concentrated on the search for a mild reagent to effect the deoxygenation of 1,4-endoxides. To this end, a series of readily accessible endoxides **17** (Scheme IV) were prepared[12] from simple furans **15** and strongly activated alkynes **16** and then subjected to deoxygenation with various oxygenophiles including triphenylphosphine, triphenylarsine, zinc dust, magnesium powder, zinc–copper couple, zinc–silver couple,[13] the aforementioned low-valent-titanium reagent,[14] and other organotitanium reagents.[15] Of all these reducing agents examined, the low-valent-titanium species emerged as the reagent of choice in terms of mildness, simplicity in execution, and product yield. The results with this reagent are summarized in Table I,[14,16] which shows that both the trifluoromethyl and ester functionalities remain intact during deoxygenation. The only notable exception was endoxide **17i**, which resulted in cycloreversion and subsequent cyclizations.[16,17]

In the course of our work along this line, Hart and Nwokogu independently reported the deoxygenation of endoxides with low-valent forms of iron and tungsten as well as titanium.[18] An example to illustrate their work is the conversion of **19** to anthracene **20** (Scheme V).[18]

Another example of the use of low-valent-titanium species in the area of natural-product synthesis is the

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(9) Norman, R. O. C.; Taylor, R. *Electrophilic Substitution in Benzenoid Compounds*; American Elsevier: New York, 1965; pp 174–182, 320–321. Olah, G. A. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley-Interscience: New York, 1963; Vol. 1, pp 91–115.

(10) For reviews, see: McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281–286. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817–826. Lai, Y.-H. *Org. Prep. Proced. Int.* **1980**, *12*, 361–391. Welzel, P. *Nachr. Chem., Tech. Lab.* **1983**, *31*, 814–816. McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405–411. Pons, J.-M.; Santelli, M. *Tetrahedron* **1988**, *44*, 4295–4312. Kahn, B. E.; Rieke, R. D. *Chem. Rev.* **1988**, *88*, 733–745.

(11) Inter alia, see: Bastide, J.; Henri-Rousseau, O. In *The Chemistry of Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley: Chichester, 1978; Part 1, pp 447–522. Nakagawa, M. In *The Chemistry of Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley: Chichester, 1978; Part 2, pp 635–712.

(12) Stork, G.; van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1953**, *75*, 384–392.

(13) Xing, Y. D.; Gong, Q. Q.; Huang, N. Z. *Huaxue Xuebao* **1983**, *41*, 934–938.

(14) Xing, Y. D.; Huang, N. Z. *J. Org. Chem.* **1982**, *47*, 140–142.

(15) Wong, C. H.; Hung, C. W.; Wong, H. N. C. *J. Organomet. Chem.* **1988**, *342*, 9–14.

(16) Wong, H. N. C.; Xing, Y. D.; Zhou, Y. F.; Gong, Q. Q.; Zhang, C. *Synthesis* **1984**, 787–790.

(17) Kobayashi, Y.; Yamashita, T.; Takahashi, K.; Kuroda, H.; Kumadaki, I. *Tetrahedron Lett.* **1982**, *23*, 343–344.

(18) Hart, H.; Nwokogu, G. *J. Org. Chem.* **1981**, *46*, 1251–1255. Hart, H.; Lai, C.-Y.; Nwokogu, G.; Shamouilian, S.; Teuerstein, A.; Zlotogorski, C. *J. Am. Chem. Soc.* **1980**, *102*, 6649–6651.

preparation of a key intermediate for fredericamycin A[19] (Scheme VI). In this work, Diels–Alder reaction between **21** and **22** gave **23**, which was deoxygenated by a mixture of $TiCl_3$, $LiAlH_4$, and Et_3N in THF to afford the highly functionalized benzene **24**.[19]

Mechanistically, the process of the deoxygenation of 1,4-endoxides with low-valent titanium is probably analogous to that proposed for the reduction of epoxides.[20] It is likely for the reduction to involve Ti(II) species, which cleave the carbon–oxygen bond of the endoxide to form a Ti(III) radical complex. Double-bond migration and reduction of Ti(III) to Ti(II) radical followed by loss of titanium(II) oxide would yield an aromatic system (Scheme VII).

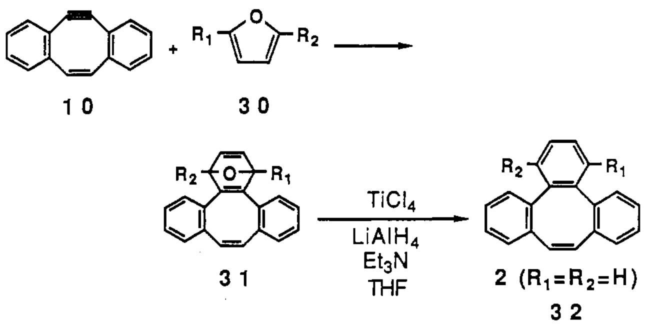
Experimentally, the ideal condition for deoxygenation of most of the endoxides examined by us required the molar ratio endoxide:$TiCl_4$:$LiAlH_4$:Et_3N = 1:7:2.5:1. The reduction of $TiCl_4$ with approximately 0.30–0.35 molar equiv of $LiAlH_4$ presumably generated some forms of Ti(II), as suggested by the black color of the reaction mixture.[21]

Encouraged by the versatility of low-valent-titanium deoxygenation in the synthesis of polyfunctional arenes, we took one step further to extend its application to the synthesis of cyclohexadiene systems such as **26** (Scheme VIII). However, treatment of the precursor **25** under the aforementioned deoxygenation conditions resulted in a mixture in which both **26** and dimethyl phthalate (**27**) were present.[22] The formation of **27** was attributable to the dehydration of **25**, which occurred readily under acidic conditions.[23] We therefore naively reasoned that this outcome might have resulted from an insufficient amount of the proton scavenger Et_3N in the reaction mixture. Accordingly, as a measure to ensure a nonacidic reaction medium, 25 molar equiv of Et_3N was used for the subsequent deoxygenation of **25**. Interestingly, essentially quantitative yield of **27** was then obtained.[22] In an effort to test the influence of Et_3N on low-valent-titanium deoxygenation, we further examined the reduction of **25** in the presence of variable amounts of Et_3N. To our surprise, the relative proportion of Et_3N played a significant role in determining the nature as well as distribution of products. In its absence, endoxide **25** underwent deoxygenation to furnish **26** without detectable contamination of **27**.[22]

The importance of the role of Et_3N in low-valent-titanium reduction was further demonstrated by the observation that, in the presence of 0.5 molar equiv of this substance, **25** was reduced yet to another set of products, namely *endo-cis*-**28** and *trans*-**29** (1:5).[24]

In the three reaction pathways mentioned above, there is so far no mechanistic support that Et_3N coordinates to the "naked" titanium species. Thus the question is still open whether such a complex is involved in any of the three distinct routes observed. Furthermore, the electron-donating character of Et_3N might also contribute to the diversified reactivities of the low-valent-titanium species. We hope that future efforts will bring some light into the current uncertainty surrounding the roles of Et_3N in these reactions.

Scheme IX



Scheme X

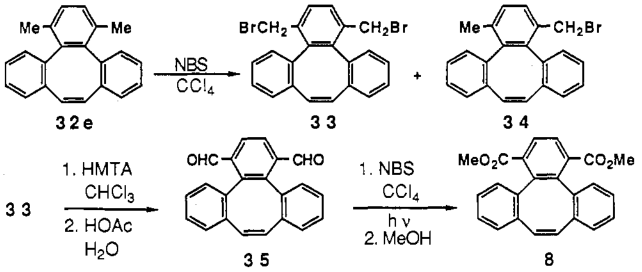


Table II

30–32	R_1	R_2	yield, % 31	yield, % 32	ref
a	H	H	51	57 (**32a** = **2**)	14
b	Me	H	not isolated	27 from **10**	26
c	CO_2Me	H	not isolated	27 from **10**	26
d	CH_2OMe	H	44	61	26
e	Me	Me	63	75	26

Synthesis of Coplanar Derivatives of Tribenzo[*a*,*c*,*e*]cyclooctene

The intriguing properties shown by coplanar cyclooctatetraenes embedded in polycyclic frameworks have recently attracted considerable attention.[25] Having accomplished in an efficient manner the deoxygenation reaction of simple 1,4-endoxides to their corresponding arenes, we henceforth sought its application to more synthetically oriented problems. As part of a program aimed at the synthesis of novel coplanar derivatives of **2** (viz., compound **6**), we have applied the low-valent-titanium reduction to the preparation of the parent **2**[14] as well as its derivatives.[26]

In view of the high reactivity of angle-strained cycloalkynes[11,27] as dienophiles, alkyne **10**[8] was chosen as a starting material. As expected, **10** reacted with a series of furans **30** to give the corresponding 1,4-endoxides **31**,[8,14,26] which were reduced by low-valent

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(19) Rao, A. V. R.; Reddy, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 574–575.

(20) McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1975**, *40*, 2555–2556. McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249–3255.

(21) van Tamelen, E. E.; Schwartz, M. A. *J. Am. Chem. Soc.* **1965**, *87*, 3277–3278.

(22) Huang, N. Z.; Xing, Y. D.; Ye, D. Y. *Synthesis* **1982**, 1041–1043.

(23) For a review on the dehydration of 7-oxabicyclo[2.2.1]heptenes to arenes, see: Wong, H. N. C.; Ng, T.-K.; Wong, T.-Y.; Xing, Y. D. *Heterocycles* **1984**, *22*, 875–890.

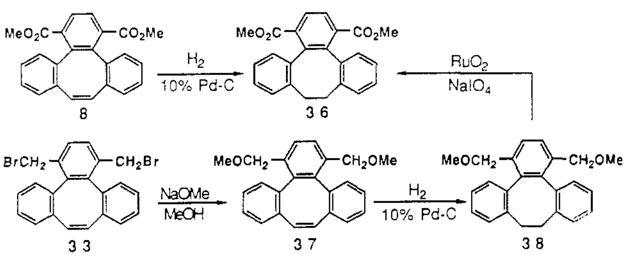
(24) Hung, C. W.; Wong, H. N. C. *Tetrahedron Lett.* **1987**, *28*, 2393–2396.

(25) Högberg, H.-E. *Acta Chem. Scand.* **1972**, *26*, 309–316. Wilcox, C. F., Jr.; Uetrecht, J. P.; Grantham, G. D.; Grohmann, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 1914–1920. Hellwinkel, D.; Reiff, G.; Nykodym, V. *Justus Liebigs Ann. Chem.* **1977**, 1013–1025. Willner, I; Rabinovitz, M. *J. Org. Chem.* **1980**, *45*, 1628–1633. Sugimoto, T.; Shibata, M.; Yoneda, S.; Yoshida, Z.-i.; Kai, Y.; Miki, K.; Kasai, N.; Kobayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 7032–7038. Mitchell, G.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 403–412.

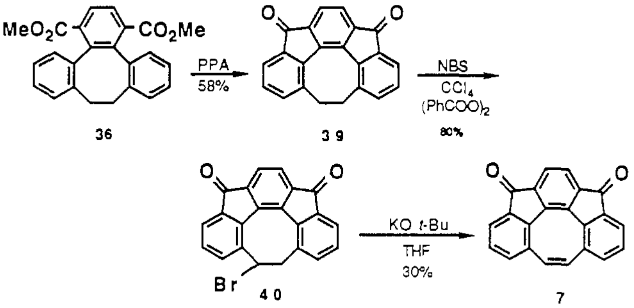
(26) Wong, H. N. C.; Hou, X. L. *Synthesis* **1985**, 1111–1115.

(27) For a recent review on angle-strained alkynes, see: Krebs, A.; Wilke, J. *Top. Curr. Chem.* **1983**, *109*, 189–233.

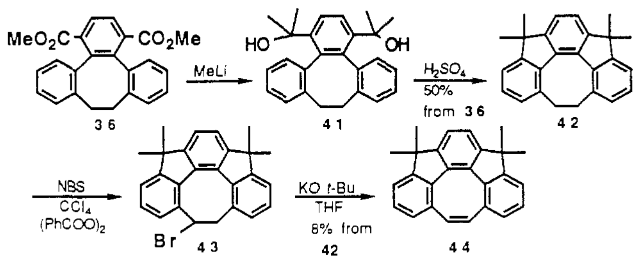
Scheme XI



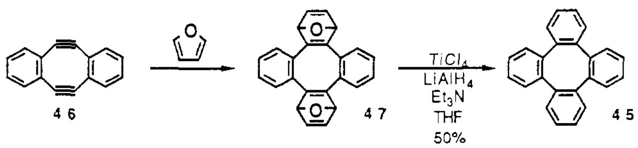
Scheme XII



Scheme XIII



Scheme XIV



titanium to afford a series of tribenzo[*a*,*c*,*e*]cyclooctenes (Scheme IX).[14,26] The results of these conversions are summarized in Table II.[14,26]

However, somewhat to our disappointment, of a number of 2,5-disubstituted furans investigated, only 2,5-dimethylfuran (**30e**) underwent successful cycloaddition with **10**. Nevertheless, the resulting **32e** could be readily transformed into **8** by the sequence outlined in Scheme X.[26] Treatment of **32e** with *N*-bromosuccinimide (NBS) provided a separable mixture of dibromide **33** and monobromide **34**,[26] and the former underwent the Sommelet reaction to give **35**, which in turn could be oxidized further to **8** (Scheme X).[26]

With **8** on hand, we were left with the seemingly simple task of preparing **7** by a Friedel–Crafts acylation procedure.[9] Unfortunately, all attempts to cyclize **8** to **7** were fruitless, presumably because of side reactions at the olefinic bond of the eight-membered ring. In a maneuver to avoid this difficulty, **8** was hydrogenated to **36**, which could also be obtained by the reaction sequence **33** → **37** → **38** → **36**, as outlined in Scheme XI.[28] Noteworthy in the latter route was the necessity to reduce **37** to **38** prior to oxidation. Otherwise, oxidative ring cleavage at the olefinic bond took place on treatment with RuO_2–$NaIO_4$.

Indeed, without the interference of the olefinic bond, polyphosphoric acid smoothly converted compound **36** to the cyclized product **39**.[28] Introduction of a bromo group to **39** was effected by reaction with NBS, from which the monobromide **40** was isolated.[28] Without purification, **40** was dehydrobrominated with KO-*t*-Bu to give the interesting polycyclic **7** as red needles (Scheme XII.)[28] Compound **7** presumably contains a coplanar eight-membered ring, which is manifested by appreciable paratropic ring currents as indicated by the unusally high field NMR signal for the olefinic protons at δ 5.83. The electronic spectrum of **7** also indicates it to be a highly conjugated system by exhibiting a bathochromic shift as well as a hyperchromic effect, as compared to noncoplanar systems such as **8**.[28]

Attempts to utilize **7** as a precursor for our targeted alkyne **6** were seriously hampered by its sparing solubility in most organic solvents. A separate effort was therefore made to search for a more soluble derivative of **7**. Toward this end, **36** was treated with excess methyllithium to furnish **41** (Scheme XIII).[28] The diol **41** was cyclized to **42** by treatment with acid. Bromination of **42** to **43** followed by dehydrobromination provided **44** as light-yellow needles. The NMR absorption signal for the olefinic protons at δ 5.91 suggests that the π-skeleton of **44** is essentially coplanar. Further confirmation of this coplanarity has been obtained by X-ray crystallographic analysis.[29]

Our efforts to convert **7** and **44** into their corresponding angle-strained alkynes (viz., **6**) have been hindered by their limited quantities at this stage. We hope that sizable amounts of these important precursors will be accumulated in due course on repeated runs or by modified preparations.

Synthesis of Benzo-Fused Derivatives of Tetraphenylene

Tetraphenylene (**45**) has been known since 1943 to form 2:1 adducts with a variety of solvent molecules.[30] In order to better understand the nature of the guest-host interaction in these inclusion compounds, we carried out systematic studies of the clathrates formed by **45** and a wide variety of guest species, ranging in size from methylene chloride to cyclohexane.[31,32] Employing our general approach to benzo-fused cyclooctatetraenes, we could readily prepare **45** by reducing **47** with low-valent titanium (Scheme XIV).[14] The endoxide **47**, in turn, was synthesized via the cycloaddition between furan and alkyne **46**.[8]

Two-fold molecular symmetry has now been recognized to assume a dominant role in the architecture of clathration lattices consolidated by van der Waals attraction and/or hydrogen bonding.[32,33] For **45**, we reasoned that a secondary C_2 axis passing through the

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[28] Hou, X. L.; Wong, H. N. C. *J. Am. Chem. Soc.* **1987**, *109*, 1868–1869.

[29] Unpublished result.

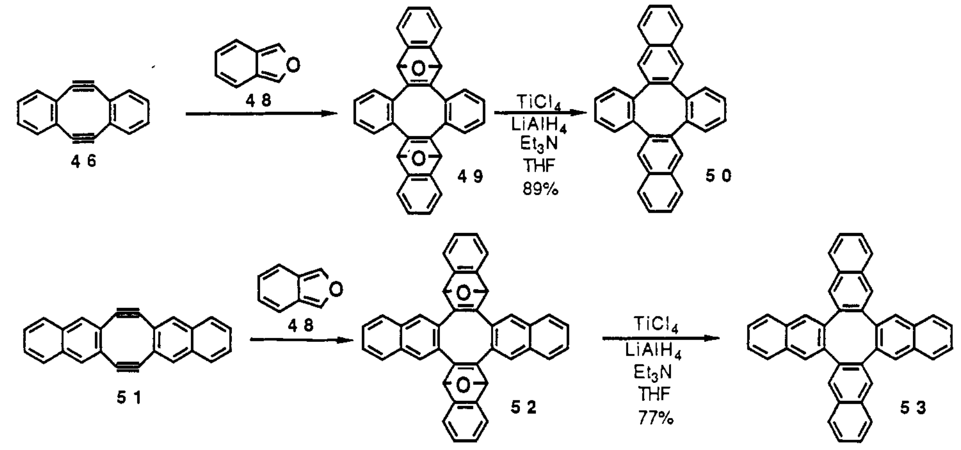
[30] Rapson, W. S.; Shuttleworth, R. G.; van Niekerk, J. N. *J. Chem. Soc.* **1943**, 326–327.

[31] Huang, N. Z.; Mak, T. C. W. *J. Chem. Soc., Chem. Commun.* **1982**, 543–544. Wong, H. N. C.; Luh, T.-Y.; Mak, T. C. W. *Acta Crystallogr., Sect. C* **1984**, *C40*, 1721–1723. Herbstein, F. H.; Mak, T. C. W.; Reisner, G. M.; Wong, H. N. C. *J. Inclusion Phenom.* **1984**, *1*, 301–308.

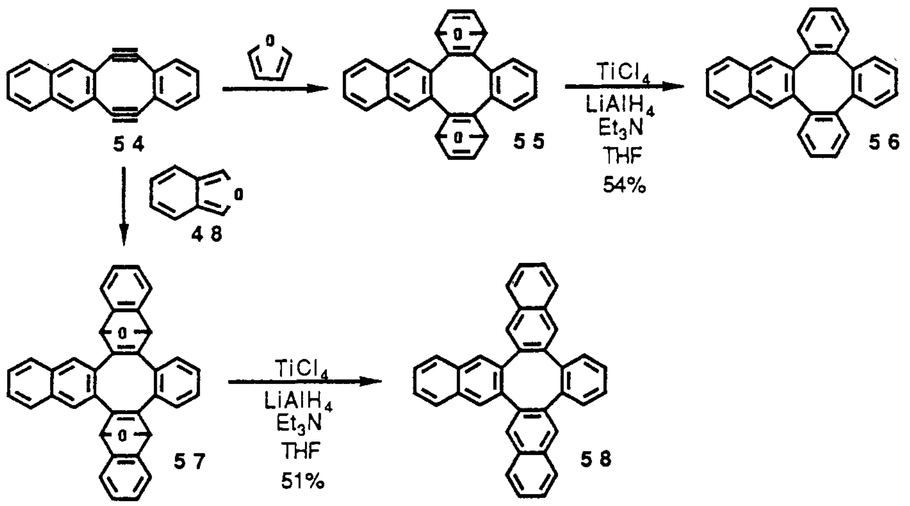
[32] For a recent review on the syntheses and inclusion properties of tetraphenylene (**45**), see: Mak, T. C. W.; Wong, H. N. C. *Top. Curr. Chem.* **1987**, *140*, 141–164.

[33] Chan, T.-L.; Mak, T. C. W.; Trotter, J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 672–675. Czugler, M.; Kálmán, A. *J. Mol. Struct.* **1981**, *75*, 29–37.

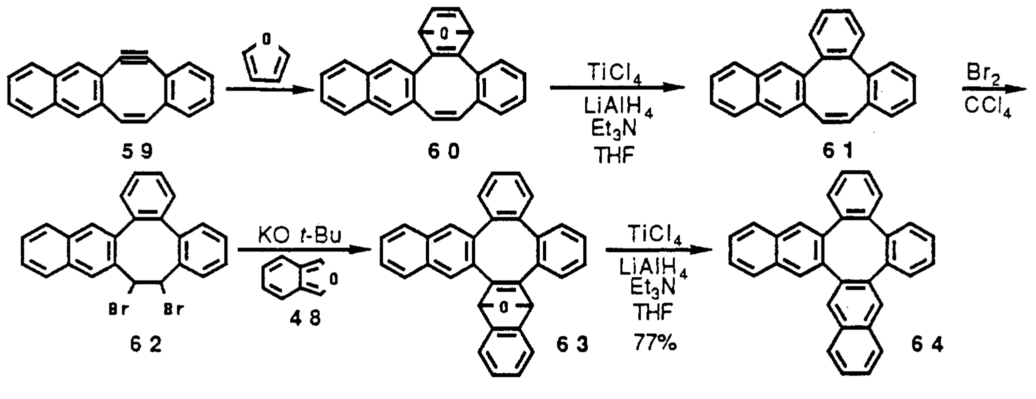
Scheme XV



Scheme XVI



Scheme XVII



centers of a pair of opposite carbon–carbon single bonds, which gives the molecule its twisted shape, would be a necessary ingredient of inclusion behavior, rather than the principal C_2 axis of the D_{2d} molecular point group. In order to test this notion, we required a series of benzo-fused tetraphenylenes for clathration with large guest molecules. Once again, the Diels–Alder reaction–deoxygenation methodology[34] provided a convenient entry to these host compounds.

Thus, **46**[8] was allowed to react with isobenzofuran (**48**),[35,36] giving **49**. Similar treatment of **51** led to **52**.[34] Low-valent-titanium reduction of **49** and **52** gave **50** and **53**, respectively (Scheme XV).[34] Similarly, **54** reacted with furan and **48**[35,36] to give **55** and **57**, which were deoxygenated to furnish **56** and **58**, respectively (Scheme XVI).[34]

The synthesis of the last member of the benzo-fused derivatives of tetraphenylene was not a trivial matter. The five-step sequence (Scheme XVII) commenced from the cycloaddition of **59** with furan. The cycloadduct **60** was deoxygenated to **61**, which was brominated to give **62**. Dehydrobromination of **62** with KO-*t*-Bu resulted in the formation of a reactive acetylene,

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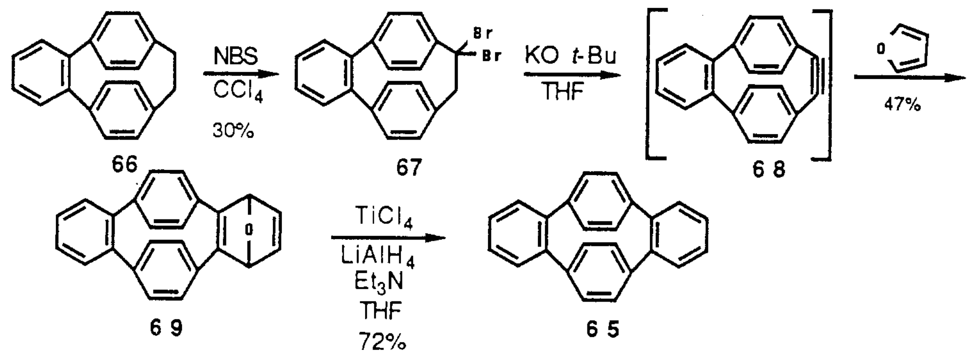
(34) Wong, H. N. C.; Man, Y.-M.; Mak, T. C. W. *Tetrahedron Lett.* **1987**, *28*, 6359–6362. Man, Y.-M.; Mak, T. C. W.; Wong, H. N. C., manuscript in preparation.

(35) Rynard, C. M.; Thankachan, C.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 1196–1201. Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061–4062.

(36) For a recent review on the chemistry of isobenzofurans, see: Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093–2135.

Scheme XVIII



which eluded isolation. However, in situ trapping of this transient intermediate was successful with **48**[35,36] to provide **63**. Again, low-valent-titanium deoxygenation transformed **63** to **64**.[34]

The realization of **50**, **53**, **56**, **58**, and **64** enabled us to investigate their inclusion behavior systematically in various organic solvents. In conformity with our previous prediction, **50**, **56**, and **58**, which do not possess a secondary C_2 axis, have exhibited no inclusion ability in all solvents examined. On the other hand, **53** and **64**, both of which contain a secondary C_2 axis, behave as effective hosts for benzene, *p*-xylene, and 1,2,4-trimethylbenzene.[34]

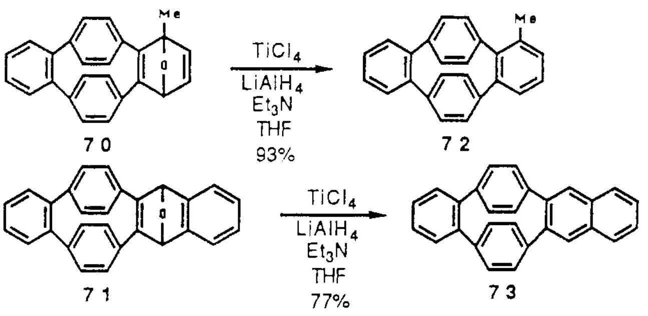
Of particular interest is **64**, whose only symmetry element is a C_2 axis. As such, **64** is resolvable into its pure optical antipodes by high-pressure liquid chromatography on a triacetylcellulose column using ethanol as eluent.[37] The determination of the inversion barrier of **64** in racemization experiments is in progress.[37]

Synthesis of Dibenzo[2.2]paracyclophane and Its Derivatives

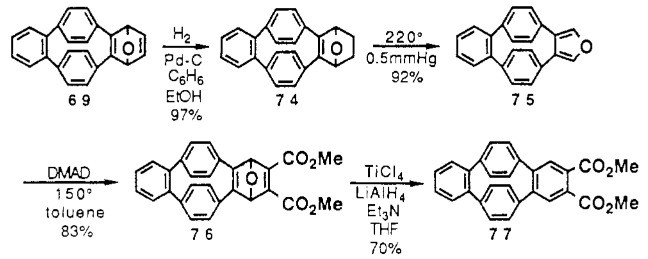
Cyclophanes have attracted considerable attention in the past three decades.[38] In the domain of physical organic chemistry, dibenzo[2.2]paracyclophane (**65**) has stood out as a unique target molecule because its rigid molecular framework should provide fixed geometry for orthogonal benzenes. In this manner, **65** represents an ideal vehicle for the study of classically conjugated but orbitally unconjugated systems.

Our approach to **65** also revolved around the combined use of the Diels–Alder reaction in conjunction with low-valent-titanium deoxygenation. Thus, the known cyclophane **66**[39] was brominated with NBS to provide **67**,[40] which was then dehydrobrominated in the usual manner to give the reactive strained alkyne **68**. As expected, **68** defied isolation but underwent cycloaddition with furan to afford **69**.[40] Low-valent-titanium reduction converted **69** into the desired **65** (Scheme XVIII).[40] It is noteworthy that the success of this synthesis hinged on the generation from **67** of the fugitive cyclophyne **68**, whose existence has been convincingly supported by independent chemical generation.[40]

Scheme XIX



Scheme XX



Similar trapping reactions of **68** with 2-methylfuran and **48**[35,36] provided **70** and **71** in 11% and 74% yields, respectively. Reduction of **70** and **71** (Scheme XIX)[40] correspondingly provided two additional diareno-fused [2.2]paracyclophanes, **72** and **73**, respectively.

In an effort to functionalize **65**, we catalytically hydrogenated **69** to **74**. Heating of **74** at 220 °C under vacuum resulted in cycloreversion to afford **75**. Subsequent cycloaddition between **75** and dimethyl acetylenedicarboxylate (DMAD) gave **76**. The diester **77** was finally obtained by deoxygenation of **76** (Scheme XX).[40]

The electronic spectrum of **65** shows intense charge-transfer bands in the 400–500-nm region,[40] indicating that the π-basicity of the para-linked benzene nuclei of **65** is larger than that of the ortho-fused benzene nuclei.[41]

The distortion of the para-linked "benzene" rings in **65** into face-to-face boat conformations as revealed by X-ray crystallographic analysis[42,43] suggests a considerable amount of molecular strain in this compound.

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(37) Sandström, J., private communications.

(38) For reviews, see: Vögtle, F.; Neumann, P. *Top. Curr. Chem.* **1971**, *48*, 67–129. Vögtle, F.; Hohner, G. *Top. Curr. Chem.* **1978**, *74*, 1–29. Boekelheide, V. *Top. Curr. Chem.* **1983**, *113*, 87–143. Vögtle, F.; Rossa, L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 515–529. Kleinschroth, J.; Hopf, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 469–480. Keehn, P. M.; Rosenfeld, S. M. *Cyclophanes*: Academic: New York, 1983; Vols. I, II.

(39) Jacobson, N.; Boekelheide, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 46–47.

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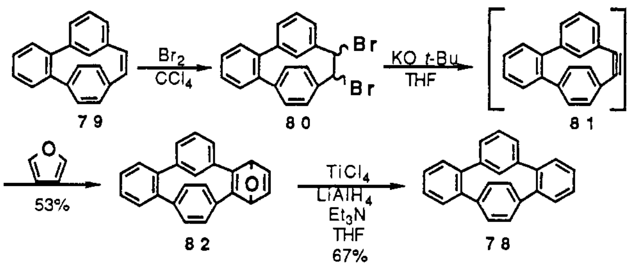
(41) Merrifield, R. E.; Phillips, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 2778–2782. Cram, D. J.; Bauer, R. H. *J. Am. Chem. Soc.* **1959**, *81*, 5971–5977.

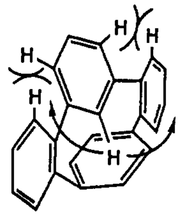
(42) Wong, H. N. C.; Chan, C. W.; Mak, T. C. W. *Acta Crystallogr., Sect. C* **1986**, *C42*, 703–705. For crystal structures of related benzo-[2.2]paracyclophane, see: Wong, H. N. C.; Chan, C. W.; Mak, T. C. W. *Jiegou Huaxue* (*J. Struct. Chem.*) **1985**, *4*, 214–217.

(43) Hope, H.; Bernstein, J.; Trueblood, K. N. *Acta Crystallogr., Sect. B* **1972**, *B28*, 1733–1743.

Scheme XXI

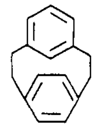
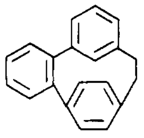
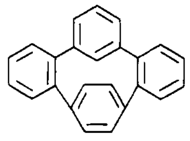
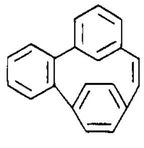
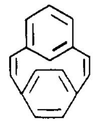


Scheme XXII



78

Table III

	T_c, °C	$\Delta G_c^{\ddagger}$, kJ/mol	NMR operating freq, MHz	ref
 **83**	140	84	60	50
	146	87	60	52
	187	92	100	51
 **85**	100	76	90	56
	116	75	250	49
 **78**	24	57	250	49
 **79**	−41	44	250	49
 **84**	−96	35	100	55

The radical anion of **65** has been studied by ESR, ENDOR, and triple-resonance spectroscopy under a variety of conditions.[44] Experimentally, the singly occupied orbital of the radical anion of **65** has been found to resemble that of the radical anion of [2.2]-paracyclophane.[45] The practical meaning of such molecular orbital similarity is the consequence that the odd electron of the radical anion of **65** is delocalized exclusively between the para-connected benzene rings.[44,45]

Photoelectron spectroscopic studies have also been carried out on **65** and **72**.[46] On the basis of a simple MO model and the compound's crystal structure,[42] tentative assignments on the orbital energies of **65** have been reported.[46] Indeed, the resulting assignments are also substantiated by the experimental data for the less symmetrical **72**.[46]

Recently, a palladium-mediated synthesis of **65** and its derivative has been reported by de Meijere.[47] Noteworthy in this new preparation is its capability to provide **65** in considerably larger quantities. Furthermore, tricarbonylchromium complexes of **65** and derivatives have also been prepared.[48]

Synthesis of Dibenzo[2.2]metaparacyclophane

The strategy for the synthesis of **65** has also been successfully applied to the synthesis of dibenzo[2.2]-metaparacyclophane (**78**) (Scheme XXI).[49] Thus, **79**[49] was converted to **80** by treatment with bromine. Dehydrobromination of **80** was effected by KO-*t*-Bu, yielding presumably **81**, which as expected eluded isolation but readily underwent cycloaddition with furan to afford **82**. The low-valent-titanium reagent was applied once again to effect the deoxygenation of **82**, from which the desired **78** was isolated.[49] The most remarkable feature in the NMR spectrum of **78** is the barely discernible appearance at 24 °C of a broad absorption signal at δ 6.95 for the four phenylic protons of the para-linked benzene ring. This unusual NMR spectral property of **78** can be attributed to the flipping process[50-53] as depicted in Scheme XXII, which has been well established for [2.2]metaparacyclophane (**83**).[54] The broad absorption at δ 6.95 clearly indicates that the signals of the four para-linked benzene protons of **78** coalesce at 24 °C, caused by the flipping of the meta-bridged benzene ring. In order to prove this, we carried out a series of variable-temperature NMR studies on **78** and **79**.[49]. The relevant data from these studies together with those previously reported for **83**,[50-53] **84**,[55] and **85**[49,56] are summarized in Table III.

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(44) Gerson, F.; Martin, W. B., Jr.; Wong, H. N. C.; Chan, C. W. *Helv. Chim. Acta* **1987**, *70*, 79–90.

(45) Gerson, F.; Martin, W. B., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 1883–1891. For a review on radical ions of cyclophanes, see: Gerson, F. *Top. Curr. Chem.* **1983**, *115*, 57–105.

(46) Yang, Z.-z.; Kovač, B.; Heilbronner, E.; Lecoultre, J.; Chan, C. W.; Wong, H. N. C.; Hopf, H.; Vögtle, F. *Helv. Chim. Acta* **1987**, *70*, 299–307. For a review on the electronic structure of cyclophanes as suggested by photoelectron spectra, see: Heilbronner, E.; Yang, Z.-z. *Top. Curr. Chem.* **1983**, *115*, 1–55.

(47) Reiser, O.; Reichow, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1277–1278. Stöbbe, M.; Reiser, O.; Näder, R.; de Meijere, A. *Chem. Ber.* **1987**, *120*, 1667–1674.

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(50) Vögtle, F. *Chem. Ber.* **1969**, *102*, 3077–3081. Vögtle, F.; Neumann, P. *Chimia* **1972**, *26*, 64–70.

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(53) Sherrod, S. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1972**, *94*, 5513–5515. Sherrod, S. A.; da Costa, R. L. *Tetrahedron Lett.* **1973**, 2083–2086. Sherrod, S. A.; da Costa, R. L.; Barnes, R. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1565–1577.

(54) Cram, D. J.; Helgeson, R. C.; Lock, D.; Singer, L. A. *J. Am. Chem. Soc.* **1966**, *88*, 1324–1325.

(55) Hylton, T. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1968**, *90*, 6887–6888. Boekelheide, V.; Anderson, P. H.; Hylton, T. A. *J. Am. Chem. Soc.* **1974**, *96*, 1558–1564.

As can be seen in Table III, the free energy of activation for the conformational flipping process ($\Delta G_c^\ddagger$) at the coalescence temperature (T_c) appears to bear intrinsic correlation with the bond types of the bridges connecting the meta-bridged benzene and the para-linked one. Boekelheide ascribed the sharply decreased energy barrier for the exchange process in **84** as compared to **83** to two chief factors: (1) the lowering of the energy of the transition state by conjugative stabilization as the meta-bridged ring becomes coplanar with the two vinyl bridges; (2) the widening of the bridge angles from 109.5° (sp^3) to 120° (sp^2) compensates the effect of bond shortening.[55] Cyclophane **78**, whose flipping transition state is lowered by conjugative stabilization and whose bridge angles are widened to 120°, was expected to show a similar value of $\Delta G_c^\ddagger$ as in **84**. However, the $\Delta G_c^\ddagger$ of **78** is found to be intermediate between those of **84** and **83**. This phenomenon may have been caused by the unfavorable nonbonded interaction between the protons of the embedded "biphenyl" structural units as **78** approaches the transition state for the conformational flipping process (Scheme XXII). Such an argument is also applicable to compounds **79** and **85**.

Concluding Remarks

Despite the lack of mechanistic information about the mode of action of the low-valent-titanium reagent, the compounds so far obtained by us through this methodology should generate sufficient stimuli for future studies. Thus, the yet to be synthesized strained alkyne **6** and its derivatives are expected to display intriguing electrical properties and might therefore quality as candidates for organic conductors.[57] Introduction of polar functional groups to the benzo-fused tetraphenylenes is anticipated to modify their abilities as host molecules in clathration. In the area of dibenzo[2.2]cyclophanes, organometallic chemistry utilizing **65** as a novel ligand is presently under investigation by us and others.[48] In addition, more accurate determination of the $\Delta G_c^\ddagger$ for **78** can be carried out with the aid of the double-irradiation technique of Forsén and Hoffman.[58] In conclusion, we have shown the combined use of Diels–Alder cycloaddition and low-valent-titanium deoxygenation to be a powerful tool in the synthesis of novel benzenoid molecules.

I wish to thank all my collaborators, whose names are mentioned in the references, for their invaluable contribution to this program, which was initiated at the Shanghai Institute of Organic Chemistry. Dr. T.-L. Chan assisted in the preparation of this Account, and his advice and suggestions are gratefully acknowledged. Thanks are also due to Prof. T. C. W. Mak for reading the manuscript and making helpful comments. I further acknowledge with thanks financial support in the form of undergraduate summer project subsidies from Chung Chi College, New Asia College, and United College of the Chinese University of Hong Kong and in the form of graduate studentships from the Croucher Foundation (Hong Kong). The Chou's Foundation also gave partial financial support to our work through the Student Campus Work Scheme administered by the Office of Student Affairs of the Chinese University of Hong Kong.

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Organoalkali Compounds by Radical Anion Induced Reductive Metalation of Phenyl Thioethers

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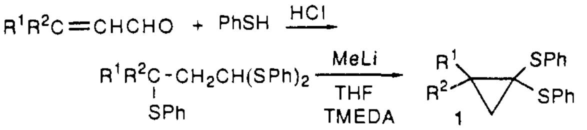
Alkyllithiums and α-Lithio Thioethers

In 1977, a visiting scientist, W. M. Daniewski, made a discovery that gave a new direction to the work in our laboratory. He found that the lithio derivatives of diphenyl dithioacetals bearing a 3-phenylthio substituent undergo a very efficient ring closure to form cyclopropanone dithioketals (e.g., eq 1).[1,2] This reaction, later shown[3] to be an intramolecular S_N2 reaction, permitted the synthesis of a variety of cyclopropanone dithioacetals.



(1)

Previous to this finding, Trost had developed a useful synthesis of cyclobutanones based on the reaction of

Theodore Cohen was born near Boston, MA, in 1929. He received his B.S. degree from Tufts College and his Ph.D. from the University of Southern California under Jerome Berson. After a year of postdoctoral work at the University of Glasgow under Derek H. R. Barton, he was appointed to the faculty of the University of Pittsburgh, where he is Professor of Chemistry. Until the mid 1970s, his major interests were in mechanistic organic chemistry in the fields of diazonium ions, copper organic chemistry, and pyridine *N*-oxides. More recently, his main interest has been in devising novel synthetic methodology, particularly in the areas of small rings, carbanions, and sulfur organic chemistry.

Mahadevan Bhupathy was born in Madras, India, in 1953. He received his B.Sc. and M.Sc. degrees from the University of Madras and served as Scientific Officer with the Department of Atomic Energy of India in the field of high-temperature thermodynamics. His Ph.D. and postdoctoral work were done at the University of Pittsburgh with Theodore Cohen in the field of construction and ring expansions of small rings and the synthesis of pheromones. He is now a Senior Research Chemist at Merck Sharp & Dohme Research Laboratories, Rahway, NJ.

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(1) Cohen, T.; Daniewski, W. M. *Tetrahedron Lett.* **1978**, 2991.

(2) Another efficient method for producing cyclopropanone dithioketals is also available starting from epoxides. Braun, M.; Seebach, D. *Chem. Ber.* **1976**, *109*, 669.

(3) Cohen, T.; Matz, J. R. *J. Org. Chem.* **1979**, *44*, 4816.

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