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ARENE 1,4-DIRADICAL FORMATION FROM o-DIALKYNYLARENES

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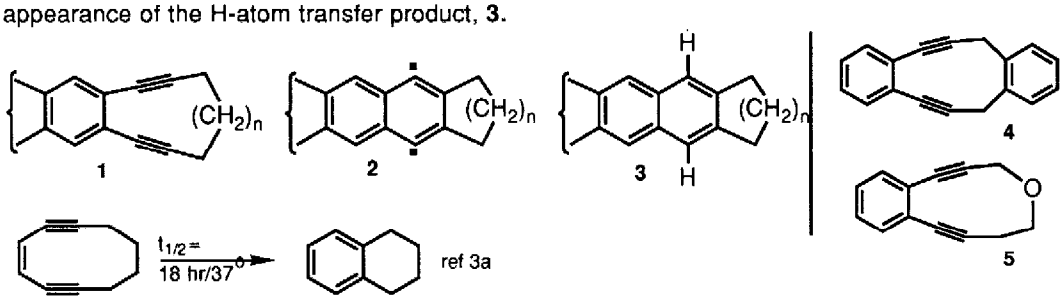
Abstract: A series of five arene and quinone derivatives with dialkynyl substituents in the ortho positions and fixed in a 10-membered ring were prepared and tested with respect to thermal rearrangement to the corresponding arene 1,4 diradicals.

The rearrangement of 1,5-diyne-3-enes to arene-1,4-diyls (Bergman rearrangement[1]) has taken on added significance with the discovery of natural toxins which appear to function by undergoing this rearrangement under mild conditions and produce DNA strand scission.[2] Models and the natural structures have been synthesized and shown to support *in vitro* this mechanistic picture for the biological effects.[2b] A limited amount of structure/reactivity information is available, largely dealing with the influence of ring size[3] and strain energy changes[3b,4] on the rate of diradical formation. In a study to determine the reactivity of o-diyne-arene analogs (**1**) of the diyne-enes, we have prepared a series of simple examples and measured the ease of rearrangement to the corresponding diyl (**2**) as determined by the disappearance of starting arene (**1**) and the appearance of the H-atom transfer product, **3**.

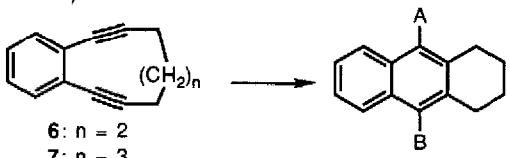


A series of related structures are already known including **4**, **5** and **6**.[5-9] The series with n=2 is particularly interesting since the corresponding 10-membered cyclic diyne-ene undergoes the Bergman rearrangement slowly at 37°C and shows DNA cleavage activity.[3a]

Starting from 1,2-dibromobenzene, 1,2-bis-(trimethylsilylethynyl)-benzene was synthesized by a Pd(0)-catalyzed reaction [2% $Pd(Ph_3P)_4$, 2% CuI, piperidine, 65°C, 15 hr] with trimethylsilylacetylene (2.3 mol-eq) in 81% yield.[10] After cleavage of the trimethylsilyl group (3 mol-eq KF, DMF-H_2O, 25°C, 4 hr, 85%), the 1,2-diethynylbenzene was converted to the dianion (2.1 mol-eq nBuLi, THF, -78°C, 1 hr) and coupled with 1,4-diiodobutane (added slowly over 0.5 hr at -78°C; warmed to 25°C, 48 hr total) to give diyne-arene **6** (56%). The corresponding 11-membered ring compound (**7**) was obtained from a similar procedure, using 1,5-diiodopentane, in 63% yield. Efforts to prepare the 9-membered ring analog (**8**) failed.

Both **6** and **7** are stable at 37°C for more than a week in dichloromethane solution. At elevated temperatures, **6** was observed to rearrange and the process showed a surprising dependence on the trapping agent. The data summarized in Table 1 show how the half-life for disappearance of **6** depends on the concentration of 1,4-cyclohexadiene (CHD, the trapping agent of choice in most

studies of the Bergman rearrangment). This dependence does not seem to have been recognized in previous work, and suggests that careful concentration measurements are necessary in order to compare data among experiments. In all cases, the mass balance is >90% and the naphthalene derivative **9** is the only product detected. The 11-membered ring analog **7** did not rearrange at a measurable rate at 84°C and decomposed to a complex mixture at higher temperatures (150-200°C).



6: n = 2
7: n = 3
8: n = 1

9: A,B=H
10: A,B=Cl
11: A,B=Br
12: A=H; B=C_6D_5
13: A=H, B=C_6H_5

Table 1. Conversion of **6** to **9** at 84°C

entry	conc of 1,4-CHD[a]	$t_{1/2}$[b]
1	0.00 M	129 hr
2	0.25 M	39 hr
3	0.50 M	24 hr
4	10.50 M (neat)	10.5 hr

a. in C_6D_6 solution.
b. based on disappearance of **6**

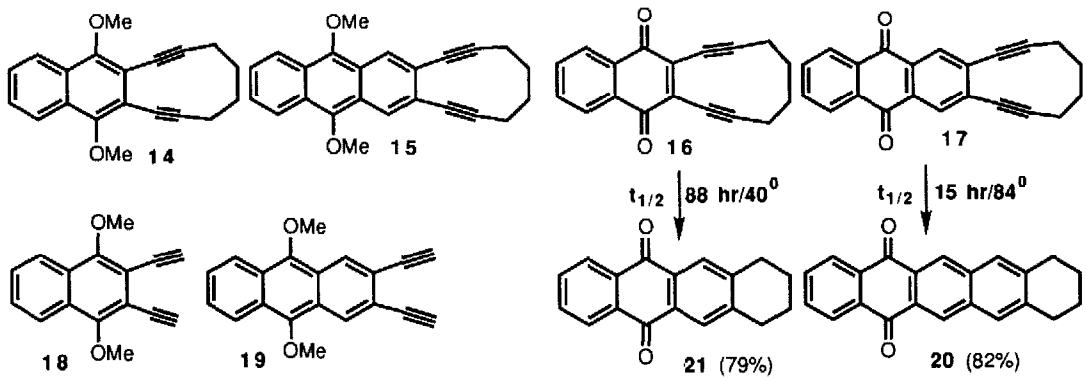
As a further test of the influence of trapping agents, **6** was mixed with CBr_4 in solution in C_6D_6. Remarkably, reaction of **6** with CBr_4 (2.5 mol-eq in C_6D_6) occurred at a reasonable rate even at 23°C and produced a mixture of bromine-containing products with no more than a trace of the expected dibromide, **11**. Reaction of the same mixture at 40°C showed loss of **6** with a half life of 18 hr, and the major product (45%) was characterized as the solvent insertion product, **12**. The same mixture at 84°C gave **12** (38%) and the expected Bergman product **11** (23%). Partly to confirm the structure of **12**, a mixture of **6** with CBr_4 was heated at reflux in C_6H_6 for 36 hr (complete conversion of **6**). Both **13** (31%) and **11** (23%) were formed. When a solution of **6** with CBr_4 (2.5 mol-eq) in C_6D_6 was immersed in a bath at 150°C for 4 hr, **11** was the only isolable product, in 57% yield.

Similarly, the disappearance of **6** at 84°C in C_6D_6 containing 2.5 mol-eq of CCl_4 showed a half-life of about 12 hr, and produced both **10** (32%) and **12** (34%), as well as the simple H-atom transfer product, **9** (22%). When the same mixture was immersed in a bath at 150°C for 4 hr, the only isolable product was **10** (61% yield).

Naphthalene (**14**) and anthracene (**15**) analogs were prepared including methoxy substituents, anticipating preparation of the corresponding quinones (**16**[12] and **17**[13]) as well. Direct coupling of 2,3-dibromo-1,4-naphthoquinone[11] with (trimethylsilyl)acetylene using the Pd/Cu catalytic system failed to give **16**. Reduction (sodium dithionite) and methylation (NaH, Me_2SO_4) gave the dimethoxy derivative (85%) which was coupled with (trimethylsilyl)acetylene in 73% yield (2.3 mol-eq $Me_3SiC{\equiv}CH$, 2% $Pd(Ph_3P)_4$, 2% CuI, piperidine, 100°C, 15 hr). Desilylation with KF at 25°C gave the bis-alkyne **18** (87%). Formation of the bis-acetylide and reaction with 1,4-diiodobutane gave the target compound, **14** (44%).

The anthracene analog, **15**, was prepared in a parallel way, starting with Friedel-Crafts reaction of o-dibromobenzene and phthalic anhydride to give 2,3-dibromo-9,10- anthroquinone in 63% yield. Direct Castro-Stephens coupling with (trimethylsilyl)acetylene again failed from the quinone, and instead the sequence of reduction (dithionite), methylation (NaH, Me_2SO_4), Pd(0) coupling, and desilylation was used to give the dialkyne **19** in 59% overall yield from the

dibromoquinone. The diacetylide anion of **19** coupled with 1,4-diiodobutane to give **15** in 62% yield. The preparation of **15** and the study of its thermal rearrangements was complicated by thermal dimerization of both **19** and **15**, and oxidative fragmentation to the quinones (e.g., **17**).[16]



The Bergman cyclization failed with the dimethoxy derivatives **14** and **15** at various temperatures up to 200°C; mixtures of decomposition products were found after many hours at that temperature. One of the decomposition products in the case of **14** was 1,2,3,4-tetrahydro-7,12-pentacenequinone (**20**), the formation of which could be explained by the dimerization and oxidative fragmentation mechanism mentioned before, followed by Bergman cyclization and H-atom transfer. The naphthoquinone and anthraquinone derivatives **16** and **17**, were prepared by oxidative demethylation of **14** and **15**, respectively, with cerium(IV) ammonium nitrate (73% and 47%). Compound **16** cyclizes at 40°C with a half-life of 88 hr in C_6D_6 in presence of 0.5M 1,4-CHD to give 1,2,3,4-tetrahydro-6,11-tetracenequinone (**21**[14]; 79%). Under the same conditions, compound **17** did not cyclize, but at 84°C the half-life was 15 hr and the analogous pentacene-quinone (**20**[15]) was isolated in 82% yield.

These data show that the aromatic structure in place of the ene unit of a diyne-ene strongly inhibits the Bergman cyclization, but that a quinone unit as in naphthoquinone **16** brings the reactivity back nearly to the level of the parent diyne-ene. In addition, the diradical formation process and trapping show unexpected features, such as a dependence on the concentration of the trapping agent (Table 1) and severe variation in product distribution with reaction temperature. Radical insertion products such as **12** and **13** and the variation in reaction rate with trapping agent (compare 1,4-cyclohexadiene and CBr_4 in reaction with **6**) have not been noted before, and suggest that the simple picture of thermal rearrangement to the arene-1,4-diyl may not be the only process occurring in these systems.[17]

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5. The parent compound in this series is **6**, which was observed as a reaction product[6] but has not been directly synthesized nor observed in the Bergman rearrangement. More unsaturated analogs rearrange to polycyclic aromatics, presumably via the appropriate diyl.[6,7] The oxa analog, **5**, has been prepared and rearranges with a half life of 52 hr at 37°C.[8] The arene analog, **4**, is suggested to rearrange rapidly under the conditions of its formation (25°C). Nicolaou has recently attached the arene-o-diyne to a model for dynemicin and observed Bergmann cyclization.[9]

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12. Characterization data for **16**: m.p. >300°C (darkens above 100°C). IR (KBr) 2942, 2932, 2190, 1666, 1595, 1369, 1323, 1301, 1204, 1006, 712 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): d 8.07 (2 H, dd, J=5.6, 3.3 Hz), 7.71 (2 H, dd, J=5.6, 3.3 Hz), 2.54-2.58 (4 H, m, 2 CH_2), 1.94-1.98 (4 H, m, 2 CH_2) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): d 180.61 (2 C=O), 139.51 (2 C), 133.99 (2 CH), 131.59 (2 C), 126.89 (2 CH), 116.26 (2 C≡C), 80.13 (2 C≡C), 28.19 (4 CH_2), 22.53 (2 CH_2) ppm. MS m/z 262 (M+, 2.93), 260 (M+, 100), 247 (48), 231 (33), 203 (39), 202 (70), 176 (22), 170 (40).

13. Characterization data for **17** m.p.>300°C (darkens above 100°C). IR (KBr) 3252, 2941, 2927, 2208, 1673, 1586, 1336, 1307, 1247, 938, 713 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): d 8.28 (2 H, dd, J=6.0, 3.3 Hz), 8.17 (s, 2 H), 7.77 (2 H, dd, J=6.0, 3.3 Hz), 2.49-2.51 (4 H, m, 2 CH_2), 1.95-1.99 (4 H, m, 2 CH_2) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): d 182.19 (2 C=O), 135.18 (2 C), 134.08 (2 CH), 133.48 (2 C), 131.81 (2 C), 127.20 (2 CH), 126.40 (2 CH), 105.25 (2 C≡C), 81.75 (2 C≡C), 28.25 (2 CH_2), 21.68 (2 CH_2) ppm. Mass spectrum, m/z 310 (M+, 100), 312 (M+, 2.31), 281 (27), 252 (50), 239 (26), 149 (36), 141 (36). MS calc.: 310.0994; found: 310.0981.

14. Characterization data for tetracenequinone **21** m.p. 209-211°C (hexane/chloro-form). IR (KBr) 2932, 2861, 1677, 1590, 1333, 1290, 960, 715 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): d 8.27 (2 H, dd, J=5.6, 3.3 Hz), 7.96 (2 H, s, CH), 7.75 (2 H, dd, J=5.6, 3.3 Hz), 2.89-2.93 (4 H, m, 2 CH_2), 1.82-1.87 (4 H, m, 2 CH_2) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): d 183.33 (2 C=0), 144.64 (2 C), 133.83 (2 CH), 133.77 (2 C), 131.02 (2 C), 131.02 (2 C), 127.93 (2 C), 127.08 (2 C), 29.83 (2 CH_2), 22.56 (2 CH_2) ppm. Mass spectrum, m/z 262 (M+, 100), 247 (45), 170 (54), 141 (58), 77 (62). MS calc.: 262.09944; found: 262.0994.

15. Characterization data for pentacenequinone **20**: m.p. 257-259°C (hexane/chloro-form). IR (KBr) 2931, 2919, 2862, 1672, 1585, 1454, 1407, 1321, 1284, 1234, 967, 716 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): d 8.70 (2 H, s, ArH), 8.36 (2 H, dd, J=5.6, 3.3 Hz), 7.79 (2 H, dd, J=5.6, 3.3 Hz), 7.76 (2 H, s, ArH), 2.98-3.01 (4 H, m, 2 CH_2), 1.85-1.90 (4 H, m, 2 CH_2) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): d 183.16 (2 C=O), 140.94 (2 C), 134.66 (2 C), 133.96 (2 CH), 133.70 (2 CH), 129.09 (2 CH), 128.88 (2C, 2CH), 127.41 (2 CH), 29.85 (2 CH_2), 22.88 (2 CH_2) ppm. MS m/z 312 (M+, 17.6), 297 (4.8), 170 (5.5), 85 (14), 83 (21).

16. The dimerization is postulated at the 9,10 position of the anthracene to give a symmetrical dimer. Exposure to air at 25° leads to an adduct which decomposes to **17** in moderate overall yield. Details of this process will be reported in the article describing this work.

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