Parallel mechanisms for the cycloaromatization of enyne allenes †

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The Myers–Saito cycloaromatization of enyne allenes is proposed to consist of two parallel mechanisms, one involving a biradical and the other with dipolar character. MCSCF calculations suggest that a nonplanar cyclic allene could be fairly close in enthalpy to the biradical, while the planar zwitterion originally proposed as a possible second intermediate is in fact a transition state for the interconversion of the two enantiomeric cyclic allenes. Competitive trapping experiments rule out the presence of a single intermediate and are consistent with the participation of parallel pathways. The reaction of (*Z*)-hepta-1,2,4-trien-6-yne in cyclopentadiene gave an inseparable mixture of two tetracyclic products whose structures were elucidated with 2-D NMR.

Introduction

The mechanism of the Myers–Saito cycloaromatization of enyne allenes is of interest because this reaction serves as a model for the key reaction of the enyne cumulene moiety in the antitumor agent neocarzinostatin.[1] The reaction is also notable for the mild conditions required to generate a reactive α,3-didehydrotoluene biradical intermediate,[2,3] and for the dual modes of reactivity that have been attributed to that intermediate.[4] As the intermediate is presumably responsible for the double hydrogen-atom abstraction that leads to the double-stranded cleavage of DNA exhibited by these model compounds,[5] a fuller understanding of the mechanism of this reaction seems relevant to the design of synthetic antitumor agents.

When Myers *et al.* pyrolyzed parent compound **1** in various trapping agents such as cyclohexa-1,4-diene (CHD), carbon tetrachloride and methanol,[4] products consistent with the presence of a biradical intermediate were observed (Fig. 1). In addition, trapping of the intermediates in methanol gave benzyl methyl ether as the major product, which was attributed to the reaction of methanol with a zwitterionic form of α,3-didehydrotoluene. Given these modes of reactivity of the intermediate, the overall mechanism for the formation of all the products observed could involve either a single biradical intermediate with some zwitterionic character or two distinct intermediates, one biradical and one displaying zwitterionic character.

Examination of solvent isotope effects on the product ratio for the reaction of **1** in methanol allowed Myers *et al.* to rule out cascade mechanisms involving initial formation of one intermediate followed by irreversible decay to the second intermediate. The rate constants for the disappearance of **1** were found to be the same in cyclohexa-1,4-diene, a medium where only biradical-like trapping products were observed, and in CD_3OH where only zwitterionic-like trapping products were observed. This could imply that the paths to the biradical products and the zwitterionic products share a rate-determining step, and thus arise from the same intermediate.

It is known that some biradicals can exhibit zwitterionic behavior,[6] but theory suggests that this should not be the case for planar α,3-didehydrotoluene. In the formalism of Salem and Rowland[7] this biradical is heterosymmetric. Each of the unpaired electrons is in an orbital that belongs to a different representation of the symmetry group of the molecule. In such species the mixing of biradical and zwitterionic electronic configurations, as required in the single-intermediate mechanism, is symmetry forbidden. The σ phenyl radical has A′ symmetry within C_s while the π benzylic radical has A″ symmetry. Thus, the $\sigma^1\pi^1$ biradical configuration has A″ symmetry and the $\sigma^2\pi^0$ zwitterionic configuration has A′ symmetry; mixing of these electronic configurations is therefore symmetry forbidden.

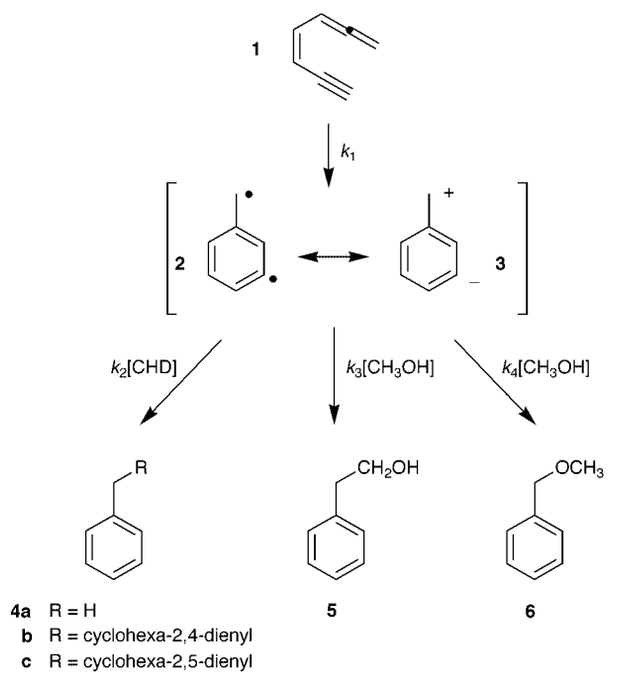
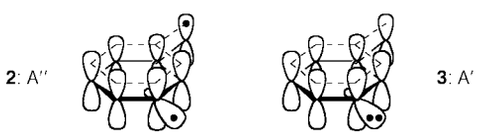


Fig. 1 Single-intermediate mechanism for the formation of trapping products from the pyrolysis of **1** in cyclohexa-1,4-diene and methanol.



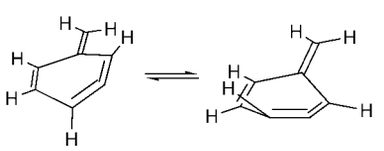
† Calculated geometries and energies of intermediates are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/1999/2291, otherwise available from BLDSC (SUPPL. NO. 57631, pp. 12) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

Table 1 Calculated energies of α,3-didehydrotoluenes[a]

Method	2	3	7	$E(3) - E(2)$	$E(7) - E(2)$	$E(3) - E(7)$
RHF/6-31G*//RHF/6-31G*	−268.39111	−268.48177[c]	−268.40898	59.9[d]	48.7[d]	11.2
RHF[b]/6-31G*//RHF[a]/6-31G*	−268.40015	—	−268.40967			6.0
MP2/6-31G*//MP2/6-31G*	−269.26436	−269.29952[c]	−269.30055	25.1[d]	2.4[d]	22.7
MP2[b]/6-31G*//MP2/6-31G*	−269.26967	—	−269.29683			17.0
CASSCF(2,2)/6-31G*//CASSCF(2,2)/6-31G*	−268.39112	−268.46200	−268.44687	44.5	9.5	35.0
CASSCF(8,8)/6-31G*//CASSCF(2,2)/6-31G*	−268.48638	−268.54669	−268.53999	37.8	4.2	33.6
CASSCF(8,8)/6-31G*//CASSCF(8,8)/6-31G*	−268.48762	—	—			
CASMP2(8,8)/6-31G*//CASSCF(2,2)/6-31G*	−269.27586	−269.33531	−269.32652	37.3	5.5	31.8
CASPT2(8,8)/6-31G*//CASSCF(2,2)/6-31G*	—	−269.35814	−269.34700		7.0	
ZPE	67.920[e]	68.577[f]	69.006[e]	0.7	1.1	0.4

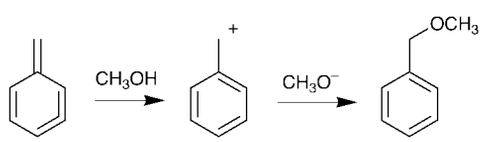
[a] Absolute energies given in hartrees, differences given in kcal mol^{-1}. [b] These calculations include the Onsager model for solvent effects. [c] These energies were obtained by the unrestricted methods, UHF and UMP2. [d] These energy differences include a 3.0 kcal mol^{-1} correction for the singlet–triplet energy gap, see text. [e] Calculated from CASSCF(2,2)/6-31G* frequencies, reported in kcal mol^{-1}. [f] Calculated from RHF/6-31G* frequencies, reported in kcal mol^{-1}.

The accessibility of the various singlet electronic states of α,3-didehydrotoluene has been considered theoretically. MRCI calculations have shown the vertical excitation energy of the singlet biradical to the lowest zwitterion to be 41 kcal mol^{-1}.[8] Bob Squires performed elegant collision-induced dissociation experiments to measure the absolute heat of formation of benzynes[9] and didehydrotoluenes, including **2**.[10] While calculating the energies of the various electronic states of the species potentially generated by these experiments, he found that the ground state closed shell structure for α,3-didehydrotoluene was in fact not planar at the RHF level of theory, but was instead a puckered cyclic allene, existing as a pair of enantiomers.[11] Simi-



7a **7b**

lar intermediates have been reported, their structures proposed on the basis of the products of their trapping.[12,13] The cyclic allene could give rise to the zwitterionic reactivity observed in methanol. For instance, the central carbon of the strained allene could be protonated by methanol, followed by nucleophilic attack of methanol on the resultant benzylic cation.



The existence and nature of the putative second intermediate have been investigated by theoretical and experimental methods, and the results form the basis of this paper.

Results and discussion

Computational results

To determine whether either the zwitterion or cyclic allene is enthalpically competitive with the singlet biradical, calculations were performed at various levels of theory including multiconfigurational complete active space (CAS) methods. Geometric parameters of the minimized geometries are provided in the supplementary material.† Energies of the biradical, planar zwitterion and cyclic allene calculated using several methods are listed in Table 1.

Single determinant Hartree–Fock wavefunctions are inappropriate for the description of singlet biradicals, and so at this level it is only possible to compare the energies of the zwitterion, cyclic allene and triplet biradical. The RHF/6-31G* method found the planar zwitterion to be 11.2 kcal mol^{-1} higher in energy than the cyclic allene. The zwitterion was found not to be a local minimum on the potential energy surface; thus when the C_s symmetry constraint was removed from the geometry optimization, the cyclic allene was obtained. A frequency calculation on the planar zwitterion revealed one imaginary frequency; it is thus a transition state for the interconversion of the cyclic allene enantiomers. The barrier height of 11.2 kcal mol^{-1} was reduced to 5.9 kcal mol^{-1} when the Onsager model was employed to capture the potentially large effect of solvent on the relative energies of **3** and **7**, but the planar zwitterion remained a saddle point on the potential energy surface.

Second order Møller–Plesset calculations placed the energy of the cyclic allene 0.6 kcal mol^{-1} lower in energy than the triplet biradical, while the planar zwitterion was 22.1 kcal mol^{-1} higher than the triplet biradical. Squires *et al.* calculated the singlet–triplet gap to be 3 kcal mol^{-1} at the MCSCF(8,8)/cc-pVDZ//MCSCF(8,8)/3-21G level of theory,[10a,14] and an inclusion of this correction puts the cyclic allene 2.4 kcal mol^{-1} above the singlet biradical. Again, the energy of the zwitterion was lowered by approximately 6 kcal mol^{-1} relative to the cyclic allene by the inclusion of the Onsager model for methanol in the MP2 method.

CASSCF(2,2), CASSCF(8,8), CASMP2(8,8), and CASPT2(8,8) single-point calculations were performed on CASSCF(2,2) minimized geometries. The geometry of the zwitterion was also minimized at the CASSCF(8,8) level since, as expected, the CASSCF(2,2) method gave an energy and geometry identical to those obtained in the RHF calculations, indicating that the (2,2) active space was dominated by a single configuration, namely the $\sigma^2\pi^0$ zwitterionic configuration. This is expected for heterosymmetric biradicals because the mixing of open-shell with closed-shell configurations is symmetry forbidden. The resulting difference between the calculated single-point energies of the CASSCF(2,2) geometry and the CASSCF(8,8) geometry was small, being only 0.8 kcal mol^{-1} for CASSCF(8,8) and 0.1 kcal mol^{-1} for CASMP2(8,8).

The zwitterion ranged from 37.3 to 44.5 kcal mol^{-1} higher in energy than the singlet biradical in the CAS calculations. The cyclic allene, however, was 9.5 kcal mol^{-1} higher than the singlet biradical from calculations employing a 2 × 2 active space, and only 4.2 kcal mol^{-1} higher using the larger 8 × 8 active space. However, inclusion of dynamic electron correlation with CASMP2(8,8) and CASPT2(8,8) methods increased this difference to 5.5 and 7.0 kcal mol^{-1}, respectively. A zero-point energy correction also raised the energy of **7** with respect to **2** by an additional 1.1 kcal mol^{-1}. These results are consistent with those obtained for cyclohexa-1,2-diene[15] using HF and MCSCF methods. The calculations suggest that the cyclic allene is more likely to be energetically competitive with the biradical than is the zwitterion, although none of the methods

Table 2 B3LYP/6-31G* energies of parent and benzannelated system intermediates

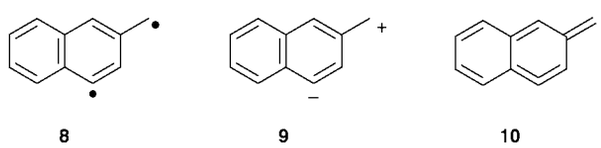
	2[a]	**3**	**7**	**8**[a]	**9**	**10**
Absolute *E*/hartrees	−270.22722	−270.15645	−270.21139	−423.87278	−423.79576	−423.84616
E relative to biradical/kcal mol^{-1}	[0]	44.4	9.9	[0]	48.3	16.7

[a] Triplet state.

predicts the near degeneracy that the experimental results would require if the cyclic allene were responsible for formation of the polar products.

It is possible that the effects of the very polar medium in which this competition is observed, methanol, are significant but are not captured in these MCSCF calculations. However, given the magnitude and uniformity of the solvent correction calculated at the RHF and MP2 levels, it seems unlikely that the large MCSCF energy differences between **2** and **7** would be mitigated by passive effects of the solvent.

Density functional calculations were performed on the triplet biradical, zwitterion and cyclic allene as well as benzannelated analogs. Calculated energies are given in Table 2. It was expected that benzannelation would destabilize the cyclic allene relative to the other intermediates, since the new ring could not



8 **9** **10**

achieve aromaticity as it could in the case of the biradical and zwitterion. In accord with the other theoretical models, B3LYP/6-31G* calculations placed the zwitterion much higher in energy than the biradical, 44.4 kcal mol^{-1} in the parent system and 48.3 kcal mol^{-1} in the benzannelated system. Benzannelation was found to selectively destabilize the cyclic allene (by 6.8 kcal mol^{-1} with respect to the triplet biradical), as expected, although the zwitterion was also somewhat destabilized (by 3.9 kcal mol^{-1}).

Competitive trapping results

Dilute methanol solutions of **1** containing varying concentrations of CHD were heated to 90 °C. The ratio of products arising from the reaction of the enyne allene with methanol was measured by GC as a function of the concentration of CHD. The results are shown in Fig. 2. The ratio of products shows a linear dependence on the concentration of CHD, with a nonzero slope.

If the single intermediate scheme depicted above (Fig. 1) were correct, then one would expect the ratio of the biradical-derived products to zwitterion-derived products to be independent of the concentration of the trapping agents present. For the scheme in Fig. 1 this ratio would be given by eqn. (1).

$$\frac{[6]}{[5]} = \frac{k_4}{k_3} \quad (1)$$

On the other hand, if the mechanism involved two rapidly interconverting intermediates (Fig. 3) the product ratio would be given by eqn. (2).

$$\frac{[6]}{[5]} = \frac{k_4}{k_5}\left(\frac{k_{-3}(k_1 + k_2) + k_1(k_5[CH_3OH] + k_6[CHD])}{k_3(k_1 + k_2) + k_2(k_4[CH_3OH])}\right) \quad (2)$$

In this case, the ratio of the benzyl methyl ether to 2-phenethanol would be linearly dependent on the concentration of CHD, as is observed in the concentration range $0 \leq [CHD] \leq 0.2$ M. It is evident from this kinetic expression that the product

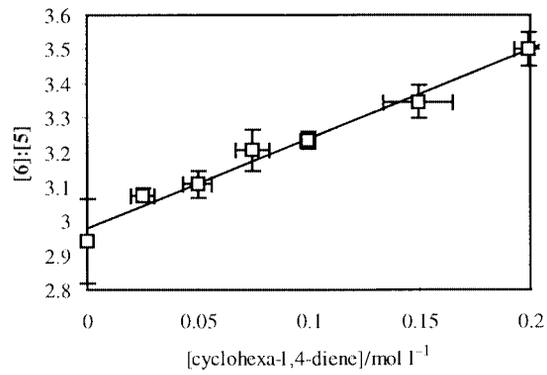


Fig. 2 Dependence of methanol product ratio on [CHD]. Ratios determined by GC, line indicates linear least squares fit to data.

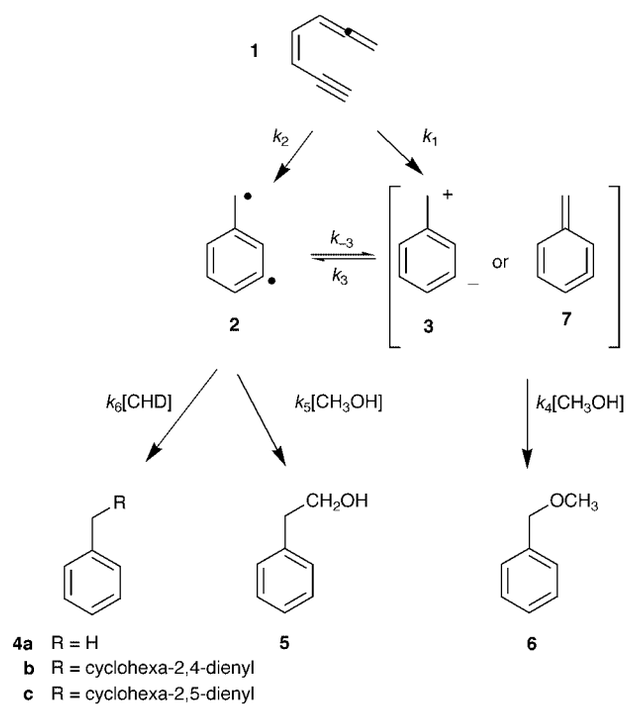


Fig. 3 Dual-intermediate mechanism for the formation of trapping products from the pyrolysis of **1** in cyclohexa-1,4-diene and methanol.

ratio is dependent on the concentration of methanol, but it is assumed that in this two-component solvent system varying low concentrations of CHD would leave the concentration of methanol essentially invariant.

It is conceivable that **6** could be formed by a direct nucleophilic attack of methanol on **1**, since this pathway would be kinetically indistinguishable from that shown in Fig. 3 at high methanol concentrations.

The dependence of the product ratio on the concentration of CHD in the 0–0.2 M range does not seem explicable as a solvent-polarity effect, since increasing the concentration of CHD should decrease the solvent polarity and thereby disfavor the polar pathway, whereas the opposite is observed.

When the concentration of CHD was increased beyond 0.2 M, the product ratio reached a maximum and then decreased.

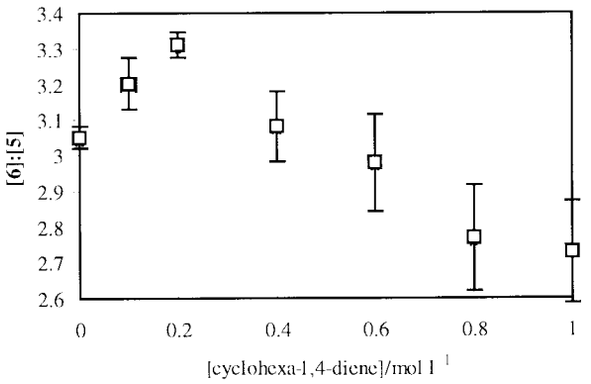


Fig. 4 Dependence of methanol product ratio on [CHD]. Ratios determined by HPLC.

This is shown in Fig. 4. When **1** was heated to 90 °C in 1:1 benzene–methanol, a ratio of **6**:**5** of 1.97 ± 0.02 was observed. Thus in a less polar solvent system without CHD trapping, the polar-pathway products decrease. On the basis of this control experiment, it seems reasonable to attribute the decrease in **6**:**5** to the changing of the solvent polarity. It is true that increasing CHD concentration from 0.2 to 1.0 M presumably involves a very modest change in polarity, but only a small change in the relative solvation energies of the two pathways would be required for the ratios observed; changing from a product ratio of 3.31 to 2.73 requires a change in the relative solvation energies of each pathway of only 0.14 kcal mol^{-1}. These results imply that the second pathway involves some polar intermediate or transition state, which at higher concentrations of nonpolar components is disfavored.

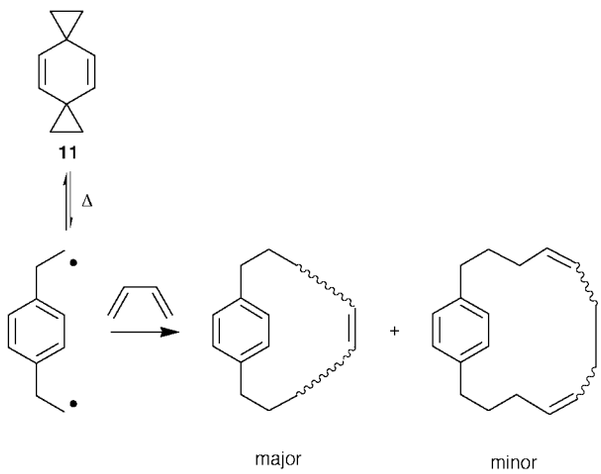
Attempts to trap a cyclic allene

Since Squires' calculations raised the possibility of the intermediacy of a cyclic allene, several attempts were made to trap this potential intermediate. Cyclic allenes are known to be very reactive Diels–Alder dienophiles,[16,17] and since it appeared that neither a biradical or a zwitterion would give rise to any Diels–Alder-like products, **1** was pyrolyzed in the presence of several dienes. Reaction of **1** with anthracene, diphenylisobenzofuran and tetraphenylcyclopentadienone gave complex product mixtures. The reaction of **1** with buta-1,3-diene and 2,3-dimethylbuta-1,3-diene gave a mixture of four products each. GC–MS revealed that each of the four products in these two mixtures had a mass corresponding to the addition of two equivalents of diene to one equivalent of enyne allene. Very clean two component product mixtures were obtained from the pyrolysis of **1** in the presence of cyclohexa-1,3-diene and cyclopentadiene. GC–MS again revealed all of these products to have come from the reaction of one molecule of **1** with two molecules of diene.

The two cyclopentadiene diadducts were purified as a mixture, but all attempts to separate the compounds by chromatographic means failed. To determine the structures of these colorless oils, 1- and 2-D NMR experiments were performed. These data are shown in Tables 3 and 4. The 1-D ^1H NMR of the mixture was complex, so the diadducts were prepared using d_6-cyclopentadiene, to determine which resonances arose from the enyne allene-derived portion of the products. The six hydrogens from **1** became hydrogens 10, 10′, 12, 13, 14 and 15 in both diadducts. The chemical shifts and coupling pattern of these hydrogens indicated that the two diadducts were α,3-disubstituted toluenes; this fragment is consistent with the known reactivity of **1**.

Heteronuclear correlation NMR experiments were performed, as these are excellent methods for resolving multiple spin systems in mixtures. One-bond connectivities were determined by HMQC, and two- and three-bond connectivities were determined using an HMBC pulse sequence. From these data, it was possible to assign the structures **14-*syn*** and **14-*anti*** to the two 2:1 cycloadducts.

The formation of these cyclophanes was unexpected, but not unprecedented. When **11** is heated, a biradical is generated which undergoes sequential addition to two butadienes to generate a cyclophane diadduct.[18] The major products of this reaction are cyclophane monoadducts, but presumably the formation of such products in the case of reactive α,3-didehydrotoluene would be sterically prohibited.



The two 2:1 cyclopentadiene cycloadducts can be distinguished by their ^1H NMRs. Molecular mechanics predicts that one of the hydrogens attached to carbon 17 in the *anti*-diadduct is placed over the aromatic ring, while no such conformational constraint is present in the *syn*-diadduct. The spin system containing the ^1H resonance at $\delta = 0.812$ can thus be assigned to the *anti*-diadduct.

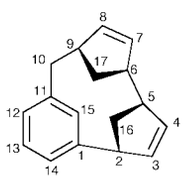
The formation of these cyclophane products explains the product mixtures observed. Reaction with cyclopentadiene and cyclohexa-1,3-diene gives two products, which correspond to the *syn*- and *anti*-configurations of the two methano-bridges. The four products obtained by trapping with butadiene and 2,3-dimethylbutadiene correspond to the *cis*, *cis*-, *cis*, *trans*-, *trans*, *cis*- and *trans*, *trans*-configurations of the two double bonds in the macrocycle. Hydrogenation of the four-component mixture of buta-1,3-diene 2:1 cycloadducts gave two products. The initial product of this hydrogenation would be expected to be [9]-*m*-cyclophane. It is known that strained [8]-*m*-cyclophane can be hydrogenated under mild conditions to the saturated hydrocarbon bicyclo[8.3.1]tetradecane.[19] The two hydrogenation products observed had masses corresponding to the addition of two and five equivalents of hydrogen, which by analogy are presumably [9]-*m*-cyclophane and bicyclo[9.3.1]-pentadecane.

Determination of mechanism of diadduct formation

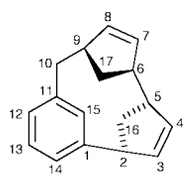
Given the unexpected products obtained from diene trapping of **1**, the question of the mechanism of their formation arises. An obvious mechanism, as suggested above, involves the sequential reaction of the biradical intermediate with two equivalents of cyclopentadiene to close the macrocycle. However, if the cyclic allene were present and a Diels–Alder reaction did occur with the diene, it is possible that bond homolysis in the cycloadduct **12** as pictured in Fig. 5 could be competitive with the 1,3-H-atom migration that would lead to a stable aromatic product. (U)B3LYP/6-31G*//(U)HF/3-21G calculations show the triplet biradical **13** resulting from such a bond homolysis to be only 1.5 kcal mol^{-1} higher in energy than the Diels–Alder adduct **12**, suggesting that such a pathway is enthalpically feasible (assuming the singlet–triplet gap in the biradical to be small).

Table 3 1- and 2-D NMR data for compound **14-*syn***

Atom	^{13}C	^{1}H (HMQC)	COSY (H,H)	HMBC (H→C)	HMBC (C→H)
1	142.96	—	—	—	2,13,16,16′
2	48.75	3.873	3,16,16′	1,3,4,5/9,15	4/7,9,14,15,16,16′
3	137.03	5.669	2,4,16,16′	5/9	2,5,16
4	131.99	5.632–5.612	3,(10′)	(2,9,16,17)	2,5,16
5	46.00	3.260–3.264	6,16′,17	3,4,6	2/3,10′,17′
6	47.09	3.302	5,9,16	—	5,8,16,16′
7	132.70	5.632–5.612	8,(10′)	(2,9,16,17)	—
8	134.86	5.696–5.680	7,17	6,17	10,10′
9	45.96	3.229–3.224	6,10	2,17	2/3,4/7,10,10′
10	36.81	2.682	10′,17	8,9,11,12,15	12,15
10′		3.047	10,4/7	8,9,11,12,15,17	
11	141.57	—	—	—	10,10′,13
12	125.15	6.786	13,15	10,14,15	10,10′,14,15
13	128.37	7.140	12,14	1,11	—
14	122.66	6.919	13,15	2,12,15	12,15
15	127.48	7.356	12,14	2,10,12,14	2,10,10′,12,14
16	34.00	1.799	2,3,6,15,16′	1,2,4,5,6	4/7
16′		2.174–2.111	2,3,5,16,17,17′	1,2,6	
17	28.70	1.167	5,8,10,16′,17′	—	4/7,8,9,10′
17′		1.922	16′,17	5	



14-*syn*



14-*anti*

Table 4 1- and 2-D NMR data for compound **14-*anti***

Atom	^{13}C	^{1}H (HMQC)	COSY (H,H)	HMBC (H→C)	HMBC (C→H)
1	146.13	—	—	—	2,13,16,16′
2	49.41	3.628	3,4,16,16′	1,3,4,5,14,15	3,4,14,15
3	130.61	5.796	2,4,16	2,9,16,17	2,4,16
4	136.65	6.233	2,3,5,16,16′	2,3,5,16	2,16
5	44.53	3.316–3.319	4,6,16′,17′	6	2,4,16
6	46.63	3.287–3.295	5,9,10,16,17′	—	5,8,16,16′,17
7	132.54	5.810	6,8	9	—
8	137.64	5.803	7,9	6,17	10,10′
9	45.19	3.242	6,8,16′,17	11	3,7,10,10′
10	36.50	2.576	10′,17	8,9,11,12,15	12,15
10′		3.171	10,15	8,9,11,12,15,17	
11	142.31	—	—	—	9,10,10′
12	126.37	6.826	13,15	10,14,15	10,10′,14,15
13	128.57	7.153	12,14	1	—
14	122.63	6.903	13,15	2,12,15	2,12,15
15	128.48	7.046	10,12,14,17′	2,10,12,14	2,10,10′,12,14
16		1.234	2,3,4,6,16′,17	1,3,4,5,6	3,4
16′	37.46	2.130–2.200	2,4,5,9,16,17,17′	1,6	
17		0.812	9,10,16,16′,17′	—	3,8,10′
17′	28.16	1.799	5,6,15,16′,17	6	

To determine which intermediate was responsible for the formation of the 2:1 cycloadduct, a competitive trapping experiment similar to that with CHD was performed. The ratio of the methanol-trapped products was measured as a function of the concentration of cyclopentadiene. The results, shown in Fig. 6, were similar to those obtained for CHD. Since the diadducts were formed at the expense of **5**, this suggests that the 2:1 cycloadducts arose from the biradical intermediate.

This result does not rule out the presence of **7**, as it is possible that the Diels–Alder reaction of **7** with cyclopentadiene was not competitive with the radical addition of **2** to the diene. The straight-line dependence of the product ratio provided further evidence that a single pathway cannot be responsible for the formation of all of the observed products.

Benzannelated α,3-didehydrotoluene

1-Ethynyl-2-(propa-1,2-dienyl)benzene (**16**) was synthesized as depicted in Fig. 7 and heated to 90 °C in methanol to examine the distribution of products. 2-Methylnaphthalene, 2-(methoxymethyl)naphthalene and 2-(naphthalen-2-yl)ethanol were observed in 1.5, 14 and 24% yields respectively. **17** and **18** arise from the biradical intermediate **8**, while **19** arises from the polar pathway. The ratio of biradical derived to polar products was 0.55, compared to ~3 for the parent system.

This reduction of products from the polar pathway was qualitatively consistent with the DFT energies calculated for the various intermediates. However, since benzannelation raised the calculated energies of both the cyclic allene and zwitterion

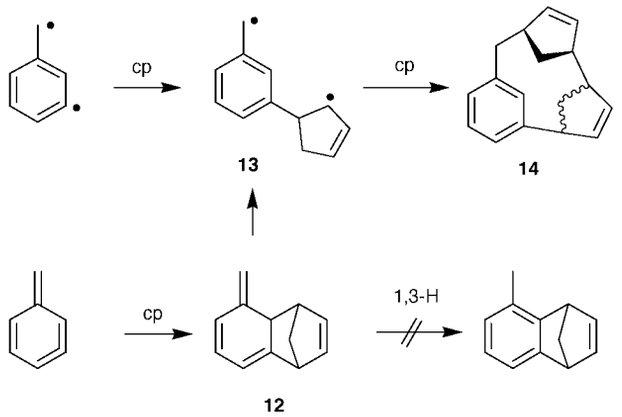


Fig. 5 Mechanisms for the formation of cyclopentadiene diadducts.

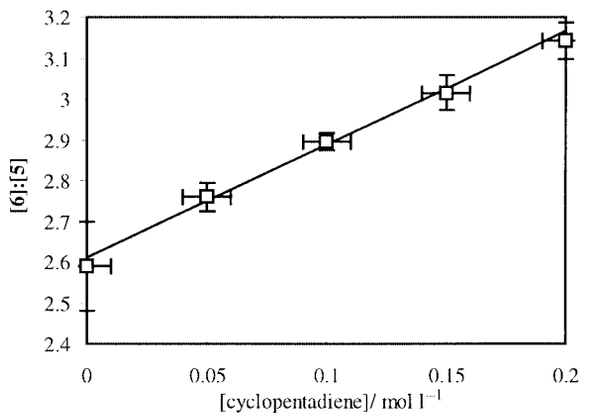


Fig. 6 Dependence of methanol product ratio on [cyclopentadiene]. Ratios determined by HPLC, line indicates linear least squares fit to data.

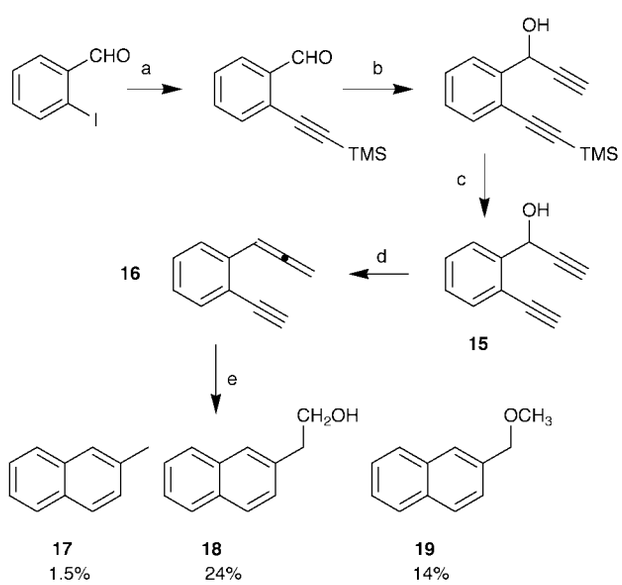


Fig. 7 Synthesis and pyrolysis of benzannelated enyne allene. Reagents and conditions: a) TMSCCH, CuI, $Pd(PPh_3)_2Cl_2$, NEt_3, Et_2O; b) HCCMgBr, Et_2O; c) K_2CO_3, CH_3OH; d) DEAD, PPh_3, *o*-nitrobenzenesulfonylhydrazine, THF;[20] e) CH_3OH, 90 °C.

relative to the triplet biradical, this result does not distinguish between those two potential intermediates. A change in the product ratio by a factor of 5.5 corresponds to a difference in free energy of 1.2 kcal mol^{-1} at 90 °C. This is much lower than the ΔEs predicted by the DFT calculations for the intermediates, which are 6.8 kcal mol^{-1} for the cyclic allene and 3.9 kcal mol^{-1} for the zwitterion, but the product ratio is also determined by the relative barrier heights of the two pathways which are undetermined.

Conclusions

The competitive trapping experiments with both CHD and cyclopentadiene are incompatible with a single intermediate mechanism and suggest that there are two parallel pathways for the cycloaromatization of **1**. While it seems fairly certain that one pathway involves the biradical **2**, the nature of the intermediate involved in the second pathway is not clear.

The cyclic allene **7** is the more likely candidate for the second intermediate based on the calculated energies for **7** and **3**. It is reasonable to assume that there could be some solvent stabilization of the zwitterion in methanol that would not be captured by the MCSCF calculations, but the 30–50 kcal mol^{-1} difference in energy seems large enough to outweigh the potential solvation energy. If the cyclic allene was present however, it is not obvious why it was not possible to trap it with dienes, as this Diels–Alder reaction is fairly efficient. The predicted product ratio for the reaction of **16** in methanol was also not in accord with that observed.

The zwitterion could be invoked as the second intermediate. The solvent effects on the product ratio in more nonpolar reaction media support a more polar intermediate, but the calculated energies seem to indicate that **3** would not be energetically competitive with the biradical. There are also polar intermediates potentially involved in the formation of **6** from **7** which could give rise to the observed solvent effects without invoking **3**. The best candidate thus appears to be the cyclic allene, but the evidence is not overwhelming. There is also the possibility that the polar pathway involves a more direct participation of the methanol, such as a direct nucleophilic attack of methanol on **1**.

A further issue needs to be resolved if two parallel mechanisms are to be proposed. If the rate determining step for the formation of products from each pathway is the same, as Myers' results seem to indicate, when does branching occur? Calculations[8,21] and experimental results[22] support an early transition state for the cyclization of **1**. MCSCF calculations indicated that the transition state still was on the closed-shell electronic surface. It is possible that a crossing to the open-shell electronic surface occurs after the transition state, and this serves as the branching point for the reaction. Thus, the branching would be post-rate determining, and therefore consistent with the rates observed.

Computational details

All *ab initio* calculations were performed using the GAUSSIAN98[23] package, save the CASPT2 and CASMP2 calculations which were performed using the MOLCAS[24] and GAMESS[25] software packages, respectively. Geometries were minimized using the 6-31G* basis set[26] at the RHF, MP2 and B3LYP levels, and using a complete active space MCSCF procedure. Calculations on biradicals at the MP2 and B3LYP levels employed the unrestricted methods and were performed on the triplet state. The zwitterion was constrained to C_s symmetry in all cases. The MCSCF geometry optimization for the planar closed-shell zwitterion ($^1A'$) was performed using two different active spaces. The smaller included just the non-bonding σ orbital and the non-bonding π orbital, while the larger included these two non-bonding orbitals as well as the three bonding π and three antibonding π orbitals. The active space employed for the MCSCF geometry optimization of the cyclic allene included the non-bonding σ and π orbitals. The CASSCF(2,2) geometry used for the planar singlet biradical ($^1A''$) was that obtained by Squires.[10a] Single-point calculations at the RHF and MP2 levels were also performed with the Onsager solvation model, which surrounds a spherical cavity containing the solute

with a continuum of constant dielectric.[27] MCSCF energies for both the planar biradical and planar zwitterion were calculated with an active space consisting of the σ and π non-bonding, the three bonding π and three antibonding π orbitals. The active space for the cyclic allene consisted of the π and π* orbitals. Single point energies were also calculated using the CAS procedure with a second order perturbative correction. Frequency calculations were performed at the RHF level for the zwitterion using the RHF minimized geometry, and at the CASSCF(2,2) level for the singlet biradical and cyclic allene. Molecular mechanics were performed using the MMX force field as implemented in PCModel.[28]

Experimental

General

(*Z*)-Hepta-1,2,4-trien-6-yne,[4] 1-(2-trimethylsilylethynylphenyl)-prop-2-yn-1-ol,[29] and *o*-nitrobenzenesulfonylhydrazine[30] were prepared as described in the literature. All reagents were used as received. Tetrahydrofuran was distilled from potassium benzophenone ketyl, methanol was distilled from magnesium methoxide and benzene was distilled from calcium hydride.

IR spectra were acquired with a Nicolet Impact 410 FT-IR spectrometer on neat samples on KBr plates. 1-D ^{1}H NMR spectra were acquired at 200 MHz on a Varian XL 200 spectrometer or at 300 MHz on a Bruker AF-300 spectrometer. ^{13}C NMR spectra were acquired at 75 MHz on a Bruker AF-300 spectrometer. 2-D COSY, HMQC and HMBC spectra were acquired on a Varian Unity 500 spectrometer. All spectra were recorded in $CDCl_3$ using TMS as a chemical shift standard. Gas chromatographs were recorded on a Hewlett-Packard 5880 GC with a flame ionization detector and a 15 m × 0.25 mm RTX-5 (5% phenylmethylpolysiloxane) fused silica capillary column. GC–mass spectra were acquired on a Hewlett-Packard 5890 GC with a Hewlett-Packard 5970 Series mass-selective detector and a 30 m × 0.25 mm DB-5 (5% phenylmethylpolysiloxane) fused silica capillary column. HPLC chromatograms were obtained on a Hewlett-Packard Series 1050 HPLC with a MWD detector and equipped with a reverse-phase HP 79916 OD Opt.574 Hypersil ODS 5 μm 200 × 4.6 mm column.

1-(2-Ethynylphenyl)prop-2-yn-1-ol (15)

0.14 g (1.013 mmol, 1.54 equiv.) of potassium carbonate was added to a solution of 0.15 g (0.657 mmol, 1.00 equiv.) of **14** in 25 ml of methanol. After stirring at room temperature for 20 minutes, TLC indicated the absence of starting material. The reaction mixture was extracted with three 25 ml portions of ethyl ether. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give 0.09 g (90% yield) of orange oil which was purified by chromatography on silica using 10% ethyl acetate in hexanes. IR: 3533.85 (br), 3396.4 (s), 3283.8 (s), 3067.8 (w), 2894.4 (w), 2118.4 (w), 2105.3 (w), 1480.5 (s), 1447.5 (m), 1274.1 (m), 1019.6 (s), 951.7 (s), 760.3 (s), 657.4 (m). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.72 (1H, d, J = 7.4 Hz), 7.52 (1H, d, J = 7.5 Hz), 7.38–7.43 (1H, m), 7.28–7.32 (1H, m), 7.52 (1H, d, J = 7.5 Hz), 5.89 (1H, d, J = 2.2 Hz), 3.39 (1H, s), 2.95 (1H, br s), 2.65 (1H, d, J = 2.2 Hz. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 63.0, 75.1, 75.7, 81.1, 83.1, 120.6, 126.9, 128.7, 129.8, 133.5, 142.5.

1-Ethynyl-2-(propa-1,2-dienyl)benzene (16)

0.18 g of DEAD (1.037 mmol, 1.35 equiv.) were added dropwise *via* syringe to an ice-cooled solution of 0.26 g PPh_3 (1.00 mmol, 1.3 equiv.) in 10 ml THF. After stirring for 10 minutes, a solution of 0.12 g of **15** (0.768 mmol, 1.0 equiv.) in 5 ml THF was added *via* syringe. After an additional 10 minutes of stirring, a solution of 0.22 g *o*-nitrobenzenesulfonylhydrazine (1.00 mmol, 1.3 equiv.) in 5 ml THF was added *via* syringe. The stirred solution was allowed to warm to room temperature over 8 hours, at which time it was concentrated *in vacuo* to thick orange oil which was eluted through a column of silica with pentane. The pentane solution was concentrated to give 50 mg (46.3% yield) of colorless oil. IR: 3289.7 (s), 3061.8 (w), 2927.8 (w), 2101.4 (w), 1938.5 (s), 1718.4 (m), 1480.5 (w), 1444.5 (m), 1060.5 (w), 855.7 (m), 758.4 (m). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.47 (1H, d, J = 8.1 Hz), 7.45 (1H, d, J = 7.5 Hz), 7.28 (1H, d × d, J = 8.1, 7.5 Hz), 7.14 (1H, d × d, J = 8.1, 7.5 Hz), 6.74 (1H, t, J = 7.0 Hz), 5.17 (2H, d, J = 7.0 Hz), 3.32 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 79.1, 82.1, 92.1, 126.7, 126.8, 129.2, 133.2 (the four quaternary carbons were not observed).

General procedure for pyrolyses

Solutions were sealed under vacuum (0.015 torr) in thick-walled glass tubes after deoxygenation by three to five freeze–pump–thaw deoxygenations. All reactions were run in a thermostatted water bath for 8–16 hours, at which time no starting material was detected. After cooling, the tubes were scored and their contents analyzed.

Competitive trapping experiments

3.55 mmolar solutions of **1** in methanol with various concentrations of cyclohexa-1,4-diene or cyclopenta-1,3-diene were sealed and heated to 90 °C for 24 hours. The product mixtures were quantified using *m*-xylene as an internal standard, using either analytical GC or HPLC.

(2*R*,5*R*,6*R*,9*S*)-Tetracyclo[9.3.1.1^{2,5}.1^{6,9}]heptadeca-1(15),3,7,11,13-pentaene and enantiomer (14-*anti*) and (2*S*,5*S*,6*R*,9*S*)-tetracyclo[9.3.1.1^{2,5}.1^{6,9}]heptadeca-1(15),3,7,11,13-pentaene and enantiomer (14-*syn*). 0.100 ml of a 70 mmolar solution of **1** in C_6D_6 was mixed with 0.100 ml of cyclopenta-1,3-diene and heated to 80 °C for 10 hours. **14 (*syn*)** and **14 (*anti*)** were produced in a 1 : 1 ratio.

14 (*syn*): MS: *m*/*z* 222 (M^+, 13%), 157 (14), 156 (100), 155 (48), 153 (10), 142 (12), 141 (66), 129 (12), 128 (30), 115 (26). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.35 (1H, s), 7.14 (1H, d × d, J = 5.9, 5.5 Hz), 6.92 (1H, d, J = 6.7 Hz), 6.79 (1H, d, J = 5.5 Hz), 5.67–5.70 (2H, m), 5.61–5.63 (2H, m), 3.87 (1H, d × d, J = 5.8, 2.0 Hz), 3.30 (1H, br s), 3.26–3.27 (1H, m), 3.22–3.23 (1H, m), 3.05 (1H, d × d, J = 12.6, 1.4 Hz), 2.68 (1H, d × d, J = 12.6, 5.1 Hz), 2.11–2.17 (1H, m), 1.80 (1H, d × m, J = 11.0 Hz), 1.92 (1H, d × d × d, J = 11.8, 8.6, 8.7 Hz), 1.17 (1H, d × d × d, J = 11.8, 2.8, 2.7 Hz).

14 (*anti*): MS: *m*/*z* 222 (M^+, 13%), 157 (14), 156 (100), 155 (41), 153 (10), 142 (11), 141 (59), 129 (11), 128 (33), 115 (26). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.15 (1H, d × d, J = 5.9, 5.5 Hz), 7.05 (1H, s), 6.90 (1H, d, J = 6.7 Hz), 6.83 (1H, d, J = 5.9 Hz), 6.23 (1H, d × d, J = 5.4, 2.0 Hz), 5.84 (2H, br s), 5.80 (1H, d × m, J = 5.4 Hz), 3.63 (1H, d × d, J = 6.3, 2.0 Hz), 3.31–3.32 (1H, m), 3.29–3.30 (1H, m), 3.24 (1H, br s), 3.17 (1H, d, J = 12.6 Hz), 2.58 (1H, d × d, J = 12.6, 7.1 Hz), 2.13–2.20 (1H, m), 1.80 (1H, m), 1.23 (1H, d, J = 11.0 Hz), 0.81 (1H, d × d × d, J = 11.8, 2.4, 2.3 Hz). The d_{12}-compounds were prepared in the same fashion, using d_6-cyclopenta-1,3-diene that was prepared by stirring cyclopenta-1,3-diene (obtained by high-temperature distillation of dicyclopentadiene) with five aliquots of a solution of sodium deuteride and DMSO. ^{1}H NMR analysis of the Diels–Alder cycloadduct of the deuterated cyclopenta-1,3-diene with *N*-methyltriazolinedione indicated that the diene had 80% deuterium incorporation.

Pyrolysis of 1 in buta-1,3-diene

Approximately 0.5 ml of buta-1,3-diene was condensed into a tube containing 0.100 ml of a 70 mmolar solution of **1** in C_6D_6. The tube was sealed and heated to 80 °C for 16 hours. GC–MS revealed four products with a mass of 198. This mixture was

concentrated *in vacuo* to remove unreacted buta-1,3-diene, and the residue dissolved in methanol. The methanolic solution was hydrogenated (40 lbs in^{-2}, 2.76×10^{-3} N m^{-2}) over palladium on carbon for 24 hours. The products of this reaction were analyzed by GC–MS, and were produced in a 60 : 40 ratio. The MS of the major product: MS: *m*/*z* 202 (M^+, 43%), 145 (26), 131 (67), 118 (58), 117 (57), 115 (29), 106 (28), 105 (60), 104 (100), 103 (29), 78 (28), 77 (26). MS of the minor product: *m*/*z* 208 (M^+, 14%), 109 (11), 97 (31), 96 (29), 95 (29), 83 (24), 82 (49), 81 (79), 79 (14), 69 (30), 68 (14), 67 (71).

Pyrolysis of 1 in 2,3-dimethylbuta-1,3-diene

0.100 ml of a 70 mmolar solution of **1** in C_6D_6 was mixed with 0.50 ml of the diene and sealed in a tube. The solution was heated to 80 °C for 10 hours. Four products with the same MS pattern were distinguished by GC–MS, which accounted for 7%, 40%, 16% and 38% of the product mixture. MS: *m*/*z* 254 (M^+, 71%), 211 (20), 170 (47), 157 (100), 155 (30), 143 (49), 142 (33), 141 (25), 129 (37), 128 (22).

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