The pentadehydro–Diels–Alder reaction

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In the classic Diels–Alder [4+2] cycloaddition reaction, the overall degree of unsaturation (or oxidation state) of the 4π (diene) and 2π (dienophile) pairs of reactants dictates the oxidation state of the newly formed six-membered carbocycle. For example, in the classic Diels–Alder reaction, butadiene and ethylene combine to produce cyclohexene. More recent developments include variants in which the number of hydrogen atoms in the reactant pair and in the resulting product is reduced by, for example, four in the tetra-dehydro-Diels–Alder (TDDA) and by six in the hexa-dehydro-Diels–Alder (HDDA) reactions. Any oxidation state higher than tetra-dehydro (that is, lacking more than four hydrogens) leads to the production of a reactive intermediate that is more highly oxidized than benzene. This increases the power of the overall process substantially, because trapping of the reactive intermediate can be used to increase the structural complexity of the final product in a controllable and versatile manner. Here we report an unprecedented overall 4π + 2π cycloaddition reaction that generates a different, highly reactive intermediate known as an α,3-dehydrotolueno. This species is in the same oxidation state as a benzyne. Like benzynes, α,3-dehydrotoluenes can be captured by various trapping agents to produce structurally diverse products that are complementary to those arising from the HDDA process. We call this new cycloisomerization process a pentadehydro-Diels–Alder (PDDA) reaction—a nomenclature chosen for chemical taxonomic reasons rather than mechanistic ones. In addition to alkynes, nitriles (RC≡N), although non-participants in aza-HDDA reactions, readily function as the 2π component in PDDA cyclizations to produce, via trapping of the α,3-(5-aza)dehydrotoluene intermediates, pyridine-containing products.

The overall oxidation states of the π-bond-containing pair of reactants in Diels–Alder processes can be viewed as the total amount of ‘dehydroness’ (see refs 10, 11) of those species (Fig. 1). This can be identified either from the overall hydrogen atom count or by the number of sp-hybridized carbon atoms that engage to create the newly formed six-membered ring (compare the carbon atoms represented by black circles and by black triangles in reactants 4 + 5 and 4 + 8 in Fig. 1). It occurred to us that a 6π-electron net [4 + 2] cycloaddition of reactants containing a total of five sp-hybridized carbon atoms—namely, an allenylene + alkyne pair like 11 + 4—might produce an α,3-dehydrotolueno (see 12, Fig. 1d). The parent species 12 itself has been characterized by photoelectron spectroscopy in the gas phase12, and derivatives of 12, which comprise a little-explored class of reactive intermediates, have been generated by black circles and by black triangles in reactants.

![Figure 1](https://example.com/figure1.png)

**Figure 1** | Terminology associated with various cyclizations in the Diels–Alder family of 4π + 2π reactions. a. The classic example of a diene (1,3-butadiene, 1) and a dienophile (ethylene, 2) reacting to give a six-membered cyclic alkene (cyclohexene, 3). b. The absence of four hydrogen atoms gives the tetra-dehydro (TDDA) variant; the product is in the benzene oxidation state. c. The absence of six hydrogen atoms gives the hexa-dehydro Diels–Alder (HDDA) variant. d. The unprecedented pentadehydro-Diels–Alder (PDDA) reaction proceeds via an α,3-dehydrotolueno (see 12); importantly, both the HDDA and PDDA reactions result in formation of trappable reactive intermediates. e. α,3-Dehydrotoluenes have previously been generated principally by cyclization of allenyl enynes like 14.
Our initial evidence for a PDDA process came from the reaction of tetrayne 15-Ms in an ambient temperature solution of piperidine. The benzylic amine 18a (Fig. 2a) was the only characterizable product formed in this experiment and was isolated in 81% yield following chromatographic purification. Tetranye 15-Ms was consumed with a half-life of approximately 15 h at room temperature. Based on several lines of evidence we have gathered and present below, we believe that the generation of 18a is best described by (i) initial, rate-limiting piperidine-catalysed isomerization of 15-Ms to produce the allenylene 16, (ii) rapid PDDA cyclization to the dehydrotoluene 17, and (iii) even more rapid trapping by protic piperidine of that reactive intermediate. We note that base-promoted isomerization of propargyl to allenyl sulfonamides is known.

This reaction process is quite distinct from the course followed during an HDDA cascade (that is, sequential benzyne formation and trapping). Formation of a product in which one of the tethering atoms separating the diyne and diynophile has become functionalized has not been observed in any HDDA cascade. We established that, in the absence of base, the tetranye 15-Ms is a well-behaved HDDA substrate, but only at elevated temperature (a half-life of ~4 h at 80 °C in C6D6). We have trapped the resulting benzene 19 with methanol or acetic acid to produce 20a or 20b, respectively (Fig. 2a). Taken together, these observations indicate that the formation of the piperidine-trapped product 18a, occurring at a substantially lower temperature, does not proceed via benzene 19. Thus, isomerization of the tetranye 15-Ms to the allene tautomer 16 occurs faster than does the thermal HDDA cyclization of 15-Ms.

The non-nucleophilic base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) mildly accelerates the initial, rate-limiting isomerization of 15-Ms to 16. The rate of formation of adduct 18a was approximately doubled (a t1/2 of 7 h versus 15 h) when five equivalents of DBU were added to the initial piperidine solution of 15-Ms. Other secondary and primary amines participate in this transformation (Fig. 2b, entries 2–5). Other amides in the tether are also compatible (entries 6 and 7), although the reaction is slower with the benzamide 15-Bz.

Oxygen nucleophiles will also trap the intermediate dehydrotoluene derivative 17 (Fig. 2b, entries 8 and 9). When carried out in methanol or aqueous acetonitrile, DBU-promoted PDDA reaction of the methanesulfonamide 15-Ms gave the methoxylated or hydroxylated adducts 18h or 18i, respectively.

We have also achieved PDDA cyclizations with substrates in which the triply bonded acceptor moiety is a cyano rather than an alkynyl group (Fig. 3a). When dissolved in neat piperidine, diynyl nitriles 21 gave rise to the pyridine derivatives 22, thereby establishing the viability of anaza-PDDA reaction. The ability of a cyano group to enter into the PDDA cyclosomeration is particularly noteworthy and decidedly distinct from its inertness to HDDA cyclization—neither we, nor others, have observed nitriles engaging in that process. This is also the case for the nitriles 21; in the absence of base, none gave evidence of cyclizing to a pyridyne such as 23, even upon heating to 150 °C in the presence of an excellent HDDA-aryne trap like acetic acid; only extensive decomposition was observed. Thus, the base-promoted tautomization to 24 and subsequent PDDA cyclosomeration of that allene to the cyano-dehydroazatoluene (or cyano-dehydroacrolein) intermediate 25 is considerably more facile than the HDDA cyclosomeration of its precursor tautomer 21. This is entirely consistent with the observation presented earlier—namely, that the PDDA cyclization of 16 is much faster than the HDDA reaction of 15-Ms (Fig. 2a).

As with the all-alkyne series already discussed (that is, 15), the nitrile substrates 21 are also competent PDDA precursors when bearing a toluenesulfonfyl, methanesulfonfyl, or benzoyl electron-withdrawing group on the propargyl nitrogen atom (Fig. 3b). Again, amines (entries 1–4), water (entries 5, 6), and alcohols (entries 7–11) are all effective trapping nucleophiles.

We have performed several experiments (Fig. 4) that provide support for the proposed mechanism for these transformations. When either of

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**Figure 2** | PDDA cascades of tetrynes. a. The first example: substrate 15-Ms undergoes base-promoted PDDA reaction and in situ trapping by piperidine to provide the adduct 18a; the HDDA cyclization of 15-Ms is slower. b. Examples indicating some of the scope of the PDDA cascades of substrates 15. 

| Entry | Tetranye substrate | Solvent (nNu-H) | Product | No. | R1 | Nu | Yield |
|-------|-------------------|----------------|---------|-----|----|-----|------|
| 1     | 15-Ms             | Piperidine     | 15-Ms   | 18a | Ms |     | 81%  |
| 2     | 15-Ms             | Pyrrolidine    | 15-Ms   | 18b | Ms |     | 73%  |
| 3     | 15-Ms             | Morpholine     | 15-Ms   | 18c | Ms |     | 82%  |
| 4     | 15-Ms             | Diethylamine   | 15-Ms   | 18d | Ms |     | 62%  |
| 5     | 15-Ms             | n-Butylamine   | 15-Ms   | 18e | Ms |     | 86%  |
| 6     | 15-Ts             | Piperidine     | 15-Ts   | 18f | Ts |     | 52%  |
| 7     | 15-Bz             | Piperidine     | 15-Bz   | 18g | Bz |     | 25%  |
| 8     | 15-Ms             | Methanol       | 15-Ms   | 18h | Ms |     | 80%  |
| 9     | 15-Ms             | MeCN/H2O       | 15-Ms   | 18i | Ms |     | 15%  |
solution at room temperature. No more than a trace amount of the expected PDIA cyclization product was observed. Instead, the enamine 31 was isolated as the principal product formed in this experiment. We presume that this arises by addition of the amine to the central carbon in allene 30 (to give a delocalized allyl/propargylic anion) rather than by direct hydroamination of the starting diyne 29; we have performed a number of HDDA reactions on diyne substrates, not activated for tautomerization, in the presence of secondary amine trapping agents and never observed amination of a conjugated diyne. The different reaction course followed by 21 compared to that of 29 can be explained by the Thorpe–Ingold effect; the lack of the geminal substituents results in a widening of the bond angle and an increase in the distance (r) between the unsaturated centres in 30. This presumably slows the rate of the PDIA cyclization, giving the piperidine time to intercept the allene. We have observed a similar phenomenon in the rate of HDDA cyclization of an analogous pair of triyne substrates and also have found computational support for this interpretation (see below, Fig. 4c).

The energy diagram in Fig. 4c shows the relevant species involved in these PDIA reactions; these are the isomeric 1,3-diynes 32, allenyne intermediates 35 and 37, diradical intermediates 36 and 38, and also have found computational support for this interpretation (see below, Fig. 4c).

Some notable points from these calculations are as follows: (i) the free energy differences between the 1,3-diynes 32a–d and tautomeric allenylenes 33a–d are small, which serves as a reminder that the potential energies of the participating functional groups in 33a–d are also high, comparable to those in 32a–d; (ii) as with triyne-to-benzyne conversions, the overall energies of reaction from 33a,b to the reactive 3,3-dehydro(aza)toluenes 37a,b are exergonic (by an amount $\Delta G^\circ$ of $\sim$35 kcal mol$^{-1}$), although not to as large an extent as those computed for HDDA cyclizations to benzenes (about $\sim$50 kcal mol$^{-1}$) (iii) the corresponding energy differences between the nitrile-containing allenylenes 33c,d and the product 3,3-dehydroazatoluenes 37c,d are even smaller, reflecting the inherently lower potential energy of a nitrile triple bond versus that of an alkyne; (iv) the magnitude of the computed free energy of activation ($\Delta G^\text{act}$) values for the first (and slower) step in the PDIA cyclization (see 34 (TS1) in Fig. 4c) are not inconsistent with the fact that our PDIA cyclizations are proceeding rapidly at less than near-ambient temperatures; and (v) the difference in the computed $\Delta G^\text{act}$ for the first step in the PDIA reaction of the nitrite 33c versus that of 33d (20.6 kcal mol$^{-1}$ versus 16.8 kcal mol$^{-1}$) is consistent with the differing behaviour of allene 24 (Fig. 3a) versus the aza-analogue 30 (Fig. 4b). We recall that the former underwent smooth PDIA cyclization to 25 en route to the piperidine-trapped adduct 22b (Fig. 3a), whereas the latter cyclized so slowly that interception by piperidine occurred to produce the enamine 31. The optimized geometries computed for the reactive conformers of 33c versus 33d (without versus with gem-dimethyl groups) differ substantially (0.21 Å) in the distance (r) between the nitrile and central allene carbons, indicating that the latter is better poised for surmounting the TS1 activation barrier.

Last, we devised an experiment to unambiguously demonstrate the intermediacy of an allene (see 40, Fig. 4d). The hydroxytetrayne 38 reacted readily with chlorodiphosphinephosphine to produce

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The table shows the results of the PDIA reactions:

| Entry | Tetrayne substrate | NuH | No. | R   | Nu   | Yield* |
|-------|-------------------|-----|-----|-----|------|--------|
| 1     | 21-Ts             | Piperidine | 22a | Ts  | pip-1 | 71%    |
| 2     | 21-Ms             | Piperidine | 22b | Ms  | pip-1 | 89%    |
| 3     | 21-Ts             | Diethylamine | 22c | Bu-1 | pipe-1 | 79%    |
| 4     | 21-Ts             | Piperidine | 22d | tBu-1 | pip-1 | 67%    |
| 5     | 21-Ts             | Water | 22e | HO | HO    | 57%    |
| 6     | 21-Ms             | Water | 22f | HO | HO    | 60%    |
| 7     | 21-Ts             | t-Butanol | 22g | HO | HO    | 57%    |
| 8     | 21-Ts             | 2-Propanol | 22h | HO | HO    | 18%    |
| 9     | 21-Ts             | Methanol | 22i | HO | HO    | 60%    |
| 10    | 21-Ms             | Methanol | 22j | HO | HO    | 72%    |
| 11    | 21-Bz             | Methanol | 22k | HO | HO    | 84%    |

Figure 3 | Cyclizations of nitrile-containing diynes—the aza-PDIA. a, Substrates 21, non-competent reactants in HDDA cyclizations, undergo smooth, base-promoted PDDA reactions to give the piperidine-trapped adducts 22a–c. Examples indicating some of the scope of the aza-PDIA cascade. *Yield of product following chromatographic purification. ^Reaction performed in a 3:1 (vol./vol.) mixture of CH$_2$Cl$_2$/water. © 2016 Macmillan Publishers Limited. All rights reserved
A solvation model (using Et₂NH) was employed (see Supplementary Information) of the directly relevant minima (32, 33, 35, and 37) and two transition state structures (34 (TS1) and 36 (TS2)) for the PDDA reaction via the diradical intermediate 35. Values beside ‘a–d’ for each of 32–37 are the computed energies (G) in kcal mol⁻¹. The 2C=CM component is either an alkyne (a, b) or a nitrile (c, d), r.d.s., rate-determining step. d. An (isolable) allenyne, the phosphine oxide 40, readily cyclizes to the benzenoid product 42.

The transient phosphinite 39, which smoothly rearranged¹⁴,²⁷ at sub-ambient temperature to the allenylidiphenylphosphine oxide 40. This labile compound was observed to degrade upon handling at room temperature, but could be rapidly purified and characterized. Dissolving 40 in methanol or water/acetonitrile gave rise spontaneously to the corresponding trapped product 42a or 42b, respectively. We view this as strong support for the intermediacy of 41 and the PDDA mechanism posited here throughout. That these reactions proceed smoothly in the absence of base also argues against a mechanism initiated by nucleophilic attack on the allene terminal carbon of the transient intermediates 16 (Fig. 2a) or 24 (Fig. 3a). The known reaction of methanol with Myers–Saito reaction-derived α,3-dehydrotoluene in similar fashion is also rate-limiting. The PDDA then proceeds rapidly, much more quickly than the HDDA cyclization of the precursor 1,3-diyne. We also have shown that the PDDA-derived dehydrotoluene, itself a reactive intermediate, can be trapped by a variety of N-, O-, and C-centred nucleophiles (Figs 2b and 3b). In one instance the conjugated allenyne has been isolated (40, Fig. 4d) and its facile cyclization and in situ trapping observed. Finally, nitriles, which do not participate in HDDA reactions, now enter the realm of reactivity, resulting in pyridine-containing products (Fig. 3).

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Figure 4 | Mechanistic aspects of the PDDA reaction. a, b. Indirect evidence for intermediacy of α,3-dehydrotoluenes and allenes. c. Relative free energies (G) from DFT calculations ((U)B3LYP-D3BJ/6-311+G(d,p); a solvation model (using Et₂NH) was employed (see Supplementary Information)) of the directly relevant minima (32, 33, 35, and 37) and two transition state structures (34 (TS1) and 36 (TS2)) for the PDDA reaction via the diradical intermediate 35. Values beside ‘a–d’ for each of 32–37 are the computed energies (G) in kcal mol⁻¹. The 2C=CM component is either an alkyne (a, b) or a nitrile (c, d), r.d.s., rate-determining step. d. An (isolable) allenyne, the phosphine oxide 40, readily cyclizes to the benzenoid product 42.
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