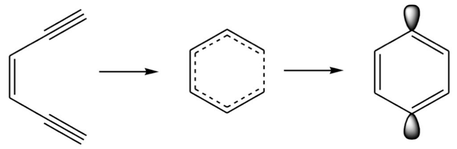
Screening Enediyne Derivatives for the Bergman Cyclization Based on the "Critical Range"

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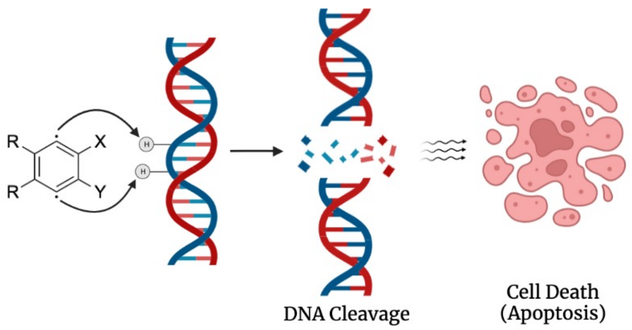
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Project Overview

Canonical Bergman cyclization of *Z*-hexa-3-ene-2,5-diyne:



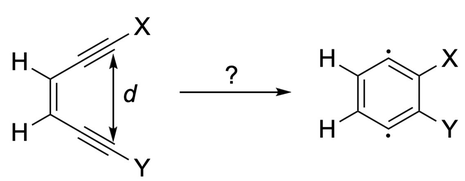
- Thermally allowed electrocyclization
- Yields aromatic diradical product *p*-benzyne, demonstrated potential for anti-tumor activity
- **"Critical Range" Hypothesis:** Spontaneous cyclization @ room temp. when C_5 & C_6 2.8–3.4 Å apart[1]



Challenge: ΔE_a = +32.8 kcal/mol for canonical Bergman[1] too high for spontaneous cyclization @ body temperature

Our ?: Could enediyne derivatives cyclize @ lower T?

Computational Methods



X, Y = F, NO_2, CN, OCH_3, OH, NH_2, H

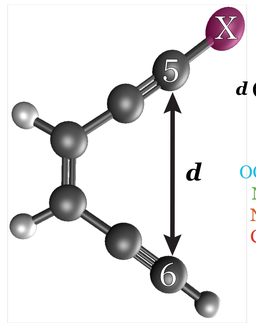
- Optimize molecular geometries for enediyne derivatives @ UB3LYP-D3M(BJ)/aug-cc-pVDZ
- Obtained CHELPG & iterative Hirschfeld atomic partial charges @ opt. geom.'s using same level of theory
- All computations performed using Q-Chem 5.4

Results w.r.t. Functionalization

Monosubstituted Enediynes

Partial Charge (a.u.) on C_5 & C_6 when X is:

CHELPG	HERSHFEILD-I
F: -0.29, 0.22	F: -0.29, 0.22
CN: -0.43, -0.36	CN: -0.25, -0.16
OH: -0.57, 0.22	OH: -0.32, 0.28
OCH3: -0.57, 0.20	OCH3: -0.32, 0.22
NO2: -0.25, -0.44	NO2: -0.15, -0.23
NH2: -0.57, 0.24	NH2: -0.33, 0.26
CH3: -0.55, 0.06	CH3: -0.31, 0.06
H: -0.49, -0.48	H: -0.29, -0.29



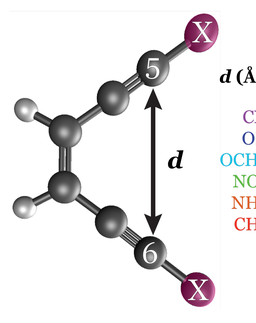
***d* (Å) when X is:**

F:	4.37
CN:	4.33
OH:	4.36
OCH3:	4.41
NO2:	4.31
NH2:	4.41
CH3:	4.39
H:	4.40

Homo (X, X) Substituted Enediynes

Partial Charge (a.u.) on C_5 & C_6 when X is:

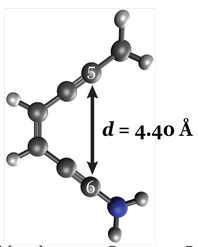
HERSHFEILD-I	CHELPG
F: 0.21, 0.21	F: 0.16, 0.16
CN: -0.12, -0.12	CN: -0.31, -0.31
OH: 0.25, 0.27	OH: 0.14, 0.19
OCH3: 0.20, 0.20	OCH3: 0.15, 0.14
NO2: -0.11, -0.11	NO2: -0.23, -0.24
NH2: 0.22, 0.22	NH2: 0.15, 0.16
CH3: 0.04, 0.04	CH3: 0.01, 0.00
H: -0.29, -0.29	H: -0.48, -0.48



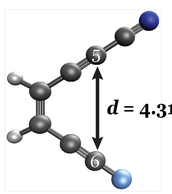
***d* (Å) when X is:**

F:	4.39
CN:	4.23
OH:	4.38
OCH3:	4.40
NO2:	4.29
NH2:	4.44
CH3:	4.36
H:	4.40

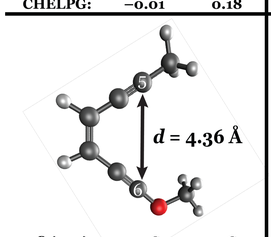
Hetero (X,Y) Substituted Enediynes



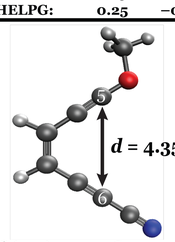
δ (a.u.)	C_5	C_6
Hirsch.-I:	0.02	0.24
CHELPG:	−0.01	0.18



δ (a.u.)	C_5	C_6
Hirsch.-I:	0.25	−0.16
CHELPG:	0.25	−0.43

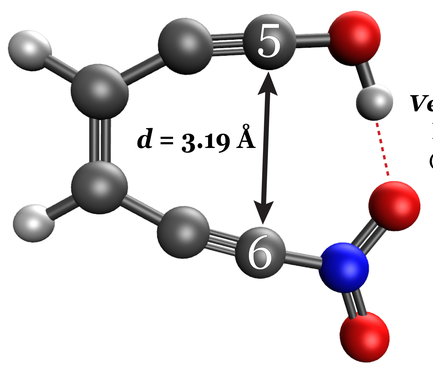


δ (a.u.)	C_5	C_6
Hirsch.-I:	0.22	0.02
CHELPG:	0.12	−0.03



δ (a.u.)	C_5	C_6
Hirsch.-I:	−0.19	0.26
CHELPG:	−0.45	0.26

- Most are similar to XH & XX w/ *d* = 4.3 ± 0.08 Å
- Opposite *δ*'s on C5 & C6 not enough to bend legs



***Very* Short H-bond @ 1.66 Å**

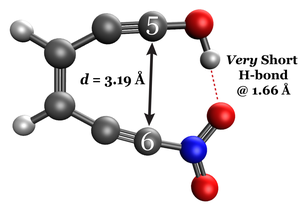
Partial Charge, *δ* (a.u.)	**C_5**	**C_6**
HERSHFELD-I:	**−0.21**	**0.42**
CHELPG:	**−0.41**	**0.35**

Notable Exceptions:

- Intramolec. X—Y attraction & opposite *δ*'s on C_5, C_6
  - (OH, NO2): *d* = 3.19 Å
  - (NH2, NO2): *d* = 3.42 Å
  - (OCH_3, NO2): *d* = 3.95 Å
- Non-examples: (OH, NH2), (OH, F), & (NH2, F)

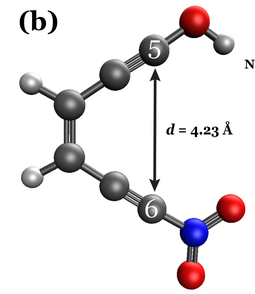
Opt. Method Matters!

(a)



Geometry optimized w/ UB3LYP-D3M(BJ)/aug-cc-pVDZ

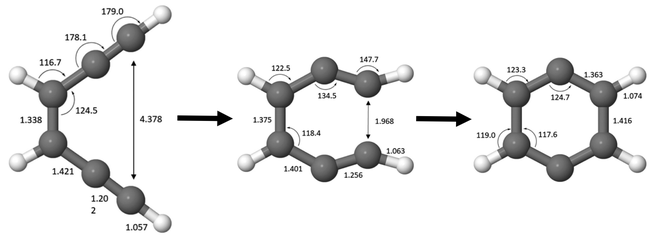
(b)



Geometry optimized w/ UB3LYP/6-311++G**

W/o X—Y attraction, opt.'s agree quite closely…but not here!

Comparing vs. Bergman



Luxon *et al.*'s SF-CCSD/cc-pVDZ canonical Bergman cyclization adapted from Figure 3 of Ref. 1

Luxon *et al.*:

- -yne terminal distance decreases by 2.41 Å from reactant → TS structure
- Our OH/NO_2 enediyne only needs to contract by 1.22 Å to cyclize…less than **half** the distortion of canonical!

Conclusions

- Mono and homo (XX) disubstituted enediynes, some hetero (XY) disubstituted enediynes similar to unsubstituted enediyne
  - –yne terminal distance *d* ~ 4.0—4.4 Å
- XY w/ intramolecular attraction b/t –yne termini reduces C_5—C_6 distance to *d* < 4.0 Å
- (OH, NO2) & (NH2, NO2) w/in critical range for spontaneous cyclization @ room temp!
- Where intramolecular interactions occur, must optimize geometries with a method that treats them accurately!

References:
1. Luxon, Orms, Kanters, Krylov, & Parish, *J. Phys. Chem. A* 122, 420 (2018)

Acknowledgements: The authors wish to acknowledge funding support from Daemen University via a Think-Tank grant (#1-059050-51520) and computational support provided by the Palmetto Supercomputing Center made available through the MERCURY consortium and the National Science Foundation (Grants CHE-1626238, CHE-1662030, and CHE-2018427).

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