Published in final edited form as:

Int J Mass Spectrom. 2015 February 1; 377: 39–43. doi:10.1016/j.ijms.2014.04.017.

Polar Effects Control the Gas-phase Reactivity of Charged *para*-Benzyne Analogs

Ashley M. Wittrig, Enada F. Archibold, Huaming Sheng, John J. Nash, and Hilikka I. Kenttämäa*

Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907 (USA)

Abstract

The gas-phase reactivity of charged *para*-benzynes is entirely unexplored as they and/or their precursors tend to undergo ring-opening upon their generation. We report here a gas-phase reactivity study of two such benzynes, the 2,5-didehydropyridinium and 5,8-didehydroisoquinolinium cations, generated in a modified dual-linear quadrupole ion trap (DLQIT) mass spectrometer. Both biradicals were found to form diagnostic products with organic molecules, indicating the presence of two radical sites. As opposed to earlier predictions that the singlet-triplet (S-T) splitting controls the radical reactivity of such species, the 2,5-didehydropyridinium cation reacts much faster in spite of its larger S-T splitting. Calculated vertical electron affinities of the radical sites of the *para*-benzynes, a parameter related to the polarity of the transition states of their reactions, appears to be the most important reactivity controlling factor.

Keywords

Dual-linear quadrupole ion trap; Ion-molecule reactions; Reactivity; *para*-Benzynes; Eneidyne; Mass spectrometry

1. Introduction

Research on the biological activity of enediyne anticancer antibiotics has been at the forefront of cancer research for many decades because of the ability of these molecules to irreversibly cleave double-stranded DNA [1–4]. The enediynes can intercalate into a double-stranded DNA molecule and undergo Bergman-cyclization to form a σ -type carbon-centered biradical intermediate, usually a *para*-benzyne analog. This highly reactive molecule can abstract a hydrogen atom from each DNA strand, causing irreversible cleavage of the double-stranded DNA and ultimately leading to apoptosis of the cell [1–4]. However, these antibiotics have been found to be extremely cytotoxic [3,5]. In order to be able to rationally

© 2014 Elsevier B.V. All rights reserved.

Fax: (+1) 765-494-0359, hilikka@purdue.edu, Homepage: <http://www.chem.purdue.edu/hilikka/>.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

design less toxic synthetic drugs, knowledge of the chemical properties of *para*-benzynes analogs is essential.

Because of their short lifetimes, high reactivity, and difficulties in generation, the chemical properties of σ -type carbon-centered aromatic σ,σ -biradicals, such as *para*-benzynes, have proven challenging to study [6–8]. One method of overcoming these challenges is the “distonic ion approach” [9–13], a technique that involves attaching a chemically inert charged group to the reactive intermediate to allow for mass spectrometric manipulation. The charged group is located on a different atom than either of the radical sites. This approach has been successfully utilized to characterize the reactivity of many *meta*-benzyne analogs in Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometers [14–16]. Unfortunately, the generation of charged *para*-benzyne analogs in FT-ICR instruments has been unsuccessful [17]. For example, the attempted generation of the radical sites in **1** and **2** (Scheme 1) via the cleavage of two iodine atoms in 2,5-diiodopyridinium and 5,8-diiodoisoquinolinium cation precursors, respectively, involved two collision-activated dissociation (CAD) events to cleave the C-I bonds in a consecutive manner. However, the monoradical intermediates formed upon loss of one iodine atom were found to undergo ring-opening faster than iodine atom loss upon CAD, eventually forming enediynes (**3** and **4**; Scheme 1) instead of the isomeric *para*-benzynes [17].

In the present study, stable *para*-benzyne analogs **1** and **2** (Scheme 1) were successfully generated in a novel dual-linear quadrupole ion trap mass spectrometer¹⁸ (DLQIT). Their reactivity toward allyl iodide, dimethyl disulfide, cyclohexane and tetra-hydrofuran is reported. To better understand the observations made for the *para*-benzyne analogs, their reactivities are compared to those of related monoradicals (Scheme 2).

2. Experimental Section

2.1 Instrumentation

All reactions were carried out in a differentially pumped dual-LQIT tandem mass spectrometer (DLQIT) [18a, 18b] equipped with a manifold for neutral reagent introduction designed based on a previously described apparatus [18c]. This instrument consists of two differentially pumped Thermo Scientific linear quadrupole ion trap (LQIT) systems that have been connected via an ion transfer octupole encased in a machined manifold. Radical and biradical iodo- precursors were introduced and ionized by protonation via atmospheric pressure chemical ionization (APCI) and the radical sites were formed by ion-source collision-activated dissociation (CAD) of iodine atoms with nitrogen collision gas. The (bi)radicals were transferred into the first linear quadrupole ion trap and allowed to react with each reagent for varying periods of time to determine reaction products and efficiencies, as previously described for FT-ICR instruments [14].

3. Results and Discussion

The reactivity of the *para*-benzynes, **1** and **2**, was expected to be similar to that of related monoradicals but lower due to the stabilizing coupling of the (singlet) biradical electrons [19,20]. When the ions having *m/z* values of **1** and **2** were allowed to react with each of the

neutral reagents, fast proton transfer was observed, indicative of the presence of the enediynes **3** and **4**, like in the earlier study [17]. The only exception was cyclohexane, which has a proton affinity too low to accept a proton from either protonated enediyne [17]. However, a second, slowly reacting isomer was also observed in each case (with the exception of cyclohexane for which only one isomer was detected). The second isomer yields reaction products similar to those of the related monoradicals. Hence, the second, slowly reacting isomers are likely to be the desired *para*-benzynes **1** and **2**. Their reactivity provides support for this hypothesis as it is analogous to that of related monoradicals, as discussed below.

Monoradicals **5**, **6**, **7**, and **8** show major reaction products, with branching ratios at or near 100%, that are diagnostic [21] for the presence of a radical site, such as a H atom abstraction product for cyclohexane and tetrahydrofuran, I atom abstraction product for allyl iodide and SCH₃ abstraction product for dimethyl disulfide (see Tables 1 and 2). The same primary reactions were observed for the *para*-benzynes. Furthermore, similar secondary reactions, identified by isolating the primary products and allowing them to react further, were observed for the *para*-benzynes with all four neutral reagents (Tables 1 and 2). This second set of abstractions reveals the presence of the second radical site, hence unambiguously demonstrating that the reacting ions are biradicals. Both biradicals show lower reactivity than the corresponding monoradicals, as expected, due to the stabilizing coupling of the nonbonding electrons in these (ground) singlet state biradicals. Many additional reaction products were also observed (Tables 1 and 2). For example, a product resulting from the addition of the entire neutral reagent molecule to the biradical was observed for all reagents with **2** and all except cyclohexane and dimethyl disulfide with **1**. In addition, a product resulting from abstraction of HSCH₃ from dimethyl disulfide was observed for both biradicals. In general, the formation of these products is an additional indication that these molecules contain a second radical site. For example, addition of tetrahydrofuran to the *para*-benzyne analogs likely occurs by initial hydrogen atom abstraction by one of the two radical sites in **1** and **2**, followed by radical-radical recombination of the remaining radical site and the newly formed reagent radical (Scheme 3). Similarly, the product resulting from abstraction of HSCH₃ from dimethyl disulfide is likely initiated by SCH₃ abstraction by the more reactive radical site followed by H atom abstraction from the eliminated SCH₃ radical by the unquenched radical site in **1** and **2** to form CH₂S.

A significantly larger amount of the enediyne isomer was observed for **1** than **2**. For **2**, ca. 2–7% of the ion population corresponds to the enediyne **4** whereas for **1**, ca. 96–98% of the ion population corresponds to the enediyne, **3**. Previous calculations have shown that during the generation of these *para*-benzyne analogs, ring opening occurs upon CAD of the monoradical precursors formed via cleavage of the first C-I bond from the diiodoprecursors [17]. Hence, the cause for the large difference in the amounts of the enediyne isomers is likely the difference in the ring-opening barriers of the relevant monoradicals [17]. Indeed, the calculated ring opening barrier for the monoradical iodoprecursor of **1**, 53.5 kcal mol⁻¹, is lower than that for **2**, 56.8 kcal mol⁻¹ (both calculated at the (U)B3LYP/6–311G(d,p)//(U)B3LYP/6–311G(d,p) level of theory). Furthermore, loss of an iodine atom from the

iodoprecursor to generate the *para*-benzyne requires more energy for **1** than **2** (65.0 and 63.5 kcal/mol, respectively) [17].

As for differences in reaction efficiencies, **1** reacts at least two orders of magnitude faster than **2** with each neutral reagent studied. The closest reaction efficiencies were found for cyclohexane, in which case **1** reacts with an efficiency of 0.1% and **2** with 0.002%. The magnitude of the S-T splitting has been used in the past to explain differences in reaction efficiencies for radical reactions of related (ground) singlet state biradicals [19,20,22,23]. Stronger coupling between the biradical nonbonding electrons has been suggested to lead to lower (radical) reactivity [19]. However, **1** and **2** do not follow the expected trend. Biradical **1** with a S-T splitting of $-4.6 \text{ kcal mol}^{-1}$ (calculated at the RHF-BCCD(T)/cc-pVTZ//UB3LYP/cc-pVTZ (singlet state) or RHF-UCCSD(T)/cc-pVTZ//UB3LYP/cc-pVTZ (triplet state) level of theory) reacts much faster than **2** with a S-T splitting of $-3.7 \text{ kcal mol}^{-1}$. However, the reactivity difference for **1** and **2** can be rationalized based on the electrophilicity of the radical sites, quantified here by the (calculated) vertical electron affinity (EA_v) of the radical sites. When the electrophilicity (i.e., calculated EA_v) increases, the transition state becomes more polarized, resulting in faster radical reactions [24–26]. With EA_v of 6.76 eV, **1** is expected to react substantially faster than **2**, with EA_v of only 5.32 eV (both values calculated at the RHF-BCCD(T)/cc-pVTZ//UB3LYP/cc-pVTZ (singlet state) or RHF-UCCSD(T)/cc-pVTZ//UB3LYP/cc-pVTZ (zwitterionic doublet state) level of theory), as observed. Hence, for the *para*-benzynes studied here, EA_v plays a more important role than the S-T splitting in controlling the reactivity.

In order to obtain more information on the reactions observed for the two biradicals with cyclohexane, the enthalpy changes associated with several reaction pathways were calculated (Scheme 4). The reactions of **1** are substantially more exothermic than those of **2**, which is in agreement with the finding of **1** being more reactive. Further, these values explain why hydride abstraction was only observed for **1** (52% branching ratio) – this reaction is exothermic for **1** but highly endothermic for **2**. Further, the predominant abstraction of two H atoms by from cyclohexane (48% branching ratio) is explained by the high exothermicity of the first abstraction, which facilitates the system to overcome any barriers associated with the second abstraction. On the other hand, the first H atom abstraction is only slightly exothermic for **2**, which may explain why the hydrogen abstraction product is the most abundant product for **2** (82% branching ratio); only a minor fraction of these monoradicals undergo a second hydrogen atom abstraction (branching ratio 8%).

Finally, the reasons for the ability to generate the *para*-benzynes in the DLQIT but not in the FT-ICR need to be considered. The activating conditions used in these two instruments are drastically different. In the FT-ICR, multiple low-energy activating collisions with argon gas were employed to slowly raise the internal energy of the monoradical precursor ions until they can overcome the lowest energy barrier, ring-opening [17]. This explains why no *para*-benzynes were generated in these experiments. In sharp contrast, in the DLQIT, diiodoprecursor ions leaving the ion source were accelerated to a poorly defined kinetic energy and allowed to undergo just a few activating collisions with nitrogen collision gas. This deposited enough internal energy into the diiodoprecursor ions to cause cleavage of

both C-I bonds. Ring opening competes with the second iodine atom cleavage but this reaction is slower (has a tighter transition state [17]) than the loss of the iodine atom to form the *para*-benzynes analogs (their activation energies are close). Hence, the presence of two isomers, the more reactive enediyne (a Brønsted acid) and the less reactive biradical, was detected in DLQIT when using reagents other than cyclohexane. The fact that only one isomer was observed when using cyclohexane is likely explained by the very low efficiencies for reactions of the two *para*-benzynes with cyclohexane (0.1% and 0.002% for **1** and **2**, respectively). This prevents the detection of the enediyne isomers that are unreactive toward this reagent due to its low proton affinity.

4. Conclusions

In conclusion, two charged *para*-benzynes analogs were successfully generated and their reactivity toward allyl iodide, cyclohexane, dimethyl disulfide and tetrahydrofuran studied in a modified dual-linear quadrupole ion trap. Primary and secondary radical reactions were observed for both *para*-benzynes and these reactions are consistent with the presence of two radical sites in each molecule. The reaction products observed for the *para*-benzynes are analogous to those of the related monoradicals although their reaction efficiencies are not as high, as expected. The two *para*-benzynes show drastically different reaction efficiencies, which can be rationalized based on a difference in the electrophilicities of their radical sites, quantified here by the (calculated) vertical electron affinity (EA_v) of the radical sites, rather than the magnitude of their S-T splittings. Further studies of these and other *para*-benzynes analogs will yield an improved understanding of the chemical properties of these important reaction intermediates. Eventually, such information may be used to rationally design anticancer drugs based on aromatic biradicals that are less cytotoxic than the enediynes.

References

1. Nicolaou KC, Dai WM. Chemistry and Biology of the Enediyne Anticancer Antibiotics. *Angew. Chem. Int. Ed.* 1991; 30:1387.
2. Nicolaou KC, Smith AL. Molecular Design, Chemical Synthesis, and Biological Action of Eneidyne. *Acc. Chem. Res.* 1992; 25:497.
3. Wenk HH, Winkler M, Sander W. One Century of Aryne Chemistry. *Angew. Chem. Int. Ed.* 2003; 42:502.
4. Gredicak M, Jeric I. Enediyne Compounds – New Promises in Anticancer Therapy. *Acta Pharm.* 2007; 57:133. [PubMed: 17507311]
5. Liu W, Christenson SD, Standage S, Shen B. Biosynthesis of the Enediyne Antitumor Antibiotic C-1027. *Science.* 2002; 297:1170. [PubMed: 12183628]
6. Wittig G. Phenyl Lithium, the Key to a New Chemistry of Organometallic Compounds. *Naturwissenschaften.* 1942; 30:696.
7. Roberts JD, Semenow DA, Simmons HE, Carlsmith LA. The Mechanism of Aminations of Halobenzenes. *J. Am. Chem. Soc.* 1956; 78:601.
8. Sander W. *meta*-Benzynes and *para*-Benzynes. *Acc. Chem. Res.* 1999; 32:669.
9. Yates BF, Bouma WJ, Radom L. Detection of the Prototype Phosphonium (CH_2PH_3), Sulfonium (CH_2SH_2) and Chloronium (CH_2ClH) Ylides by Neutralization-reionization Mass Spectrometry: a Theoretical Prediction. *J. Am. Chem. Soc.* 1984; 106:5805.
10. Yates BF, Bouma WJ, Radom L. Distonic Radical Cations: Guidelines for the Assessment of Their Stability. *Tetrahedron.* 1986; 42:6225.

11. Hammerum S. Distonic Radical Cations in Gaseous and Condensed Phase. *Mass Spectrom. Rev.* 1988; 7:123.
12. Kenttämäa HI. Long-Lived Distonic Radical Cations. *Org. Mass Spectrom.* 1994; 29:1.
13. Smith RL, Kenttämäa HI. A General Method for the Synthesis of Charged Phenyl Radicals in the Gas Phase. *J. Am. Chem.* 1995; 117:1393.
14. Jankiewicz BJ, Vinueza NR, Kirkpatrick LM, Gallardo VA, Li G, Nash JJ, Kenttämäa HI. Does the 2,6-Didehydropyridinium Cation Exist? *J. Phys. Org. Chem.* 2013; 26:707.
15. Thoen KK, Kenttämäa HI. Synthesis and Characterization of Aromatic Biradicals in the Gas Phase: a meta-Benzyne with an Inert Positively Charged Substituent and Its *ortho*- and *para*-Isomers. *J. Am. Chem. Soc.* 1997; 119:3832.
16. Price JM, Kenttämäa HI. Characterization of Two Chloro-Substituted *m*-Benzyne Isomers: Effect of Substitution on Reaction Efficiencies and Product. *J. Phys. Chem. A.* 2003; 107:8985.
17. Kirkpatrick LM, Vinueza NR, Jankiewicz BJ, Gallardo VA, Archibold EA, Nash JJ, Kenttämäa HI. A Study of Three Gaseous *para*-Benzyne Analogs. *Chem. Eur. J.* 2013; 19:9022. [PubMed: 23703949]
18. (a) Owen, BC. Ph.D. Thesis. Purdue University; 2012. (b) Owen BC, Jarrell TM, Schwartz JC, Oglesbee R, Carlsen M, Archibold EA, Kenttämäa HI. Differentially Pumped Dual Linear Quadrupole Ion Trap (DLQIT) Mass Spectrometer: A Mass Spectrometer Capable of Clean MSⁿ Experiments. *Anal. Chem.* 2013; 85:11284. [PubMed: 24171553] (c) Gronert S. Estimation of Effective Ion Temperatures in a Quadrupole ion trap. *J. Am. Soc. Mass Spectrom.* 1998; 9:845.
19. Logan CF, Chen PJ. Ab Initio Calculations of Hydrogen Abstraction Reactions of Phenyl Radical and *p*-Benzyne. *J. Am. Chem. Soc.* 1996; 118:2113.
20. Roth WR, Hopf H, Wasser T, Zimmerman H, Werner C. 1,4-Didehydronaphthalin. *Liebigs Ann.* 1996:1691.
21. Jankiewicz BJ, Reece JN, Vinueza NR, Nash JJ, Kenttämäa HI. Reactivity of the 3,4,5-Tridehydropyridinium Cation, an Aromatic σ,σ,σ -Triradical. *Angew. Chem. Int. Ed.* 2008; 47:9860.
22. Nash JJ, Kenttämäa HI, Cramer CJ. Quantum Chemical Characterization of the Structures, Thermochemical Properties, and Singlet-Triplet Splittings of Didehydroquinolinium and Didehydroisoquinolinium Ions. *J. Phys. Chem. A.* 2005; 109:10348. [PubMed: 16833330]
23. Clark AE, Davidson ER. Model Studies of Hydrogen Atom Addition and Abstraction Processes Involving *ortho*-, *meta*-, and *para*-Benzynes. *J. Am. Chem. Soc.* 2001; 123:10691. [PubMed: 11674001]
24. Jing LH, Nash JJ, Kenttämäa HI. Correlation of Hydrogen-Atom Abstraction Reaction Efficiencies for Aryl Radicals with their Vertical Electron Affinities and the Vertical Ionization Energies of the Hydrogen Atom Donors. *J. Am. Chem. Soc.* 2008; 130:17697. [PubMed: 19061320]
25. Clarke JS, Rypkema HA, Kroll JH, Donahue NM, Anderson JG. Multiple Excited States in a Two-State Crossing Model: Predicting Barrier Height Evolution for H + Alkene Addition Reactions. *J. Phys. Chem. A.* 2000; 104:4458.
26. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*. New York: Wiley; 1995.

1 **3** **2** **4****Scheme 1.**

para-Benzynes **1** and **2** and the corresponding enediyne isomers **3** and **4**

Scheme 2.
The monoradicals studied

Scheme 3.

Proposed mechanism for the addition of tetrahydrofuran to **2**

Scheme 4.

Calculated enthalpy changes for various reaction pathways with cyclohexane for **1** (left) and **2** (right)

Table 1

Reaction Efficiencies^a and Branching Ratios^{b,c,d} for 2,5-Didehydropyridinium^e (1), 2-Dehydropyridinium^e (6) and 3-Dehydropyridinium^e (7) Cations With Several Neutral Reagents

EA ^f (eV)	5.94	6.55	6.76
S-T Splitting ^g (kcal/mol)	--	--	-4.6
Addition	57%	86%	I Abs
Allene Abs ^g	20%	14%	Allyl Abs
Abs	17%		
2° I Abs			
2° H Abs			
Allyl Abs	7%		
Efficiency = 0.9% <i>para</i> -benzynes ^d	2%	Efficiency = 54%	Efficiency = 52%
SCH ₃ Abs	40%	SCH ₃ Abs	SCH ₃ Abs
2° SCH ₃ Abs		e ⁻ Abs	H Abs
HSCH ₃ Abs	34%	H Abs	2%
e ⁻ Abs	14%	SSCH ₃ Abs	1%
2° SCH ₃ Abs			
SCH ₂ Abs	7%		
SSCH ₃ Abs	5%		
2° SCH ₃ Abs			
Efficiency = 0.8% <i>para</i> -benzynes ^d	2%	Efficiency = 90%	Efficiency = 83%

H ₂ O Abs	33%	H Abs	100%	H Abs	99%
	Hydride Abs	29%			CH ₂ Abs	
	CH ₂ O Abs	13%			C ₂ H ₃ Abs	
	2° 2xH Abs				CH ₂ O Abs	
	Addition	15%			C ₃ H ₆ Abs	
	C ₂ H ₄ O Abs	7%				
	H Abs	4%				
	2° H abs					(The last four products have a total abundance of 1%)
Hydride Abs	52%	H Abs	100%	H Abs	100%
	2xH Abs	48%				
	H ₂ O Abs ^d					
	OH Abs ^d					
	Efficiency = 0.1% (only <i>para</i> -benzynes present)			Efficiency = 46%		Efficiency = 20%

^a Reaction efficiencies calculated from least-squares non-linear fits of the pseudo-first order rate plots and are reported as $k_{\text{exp}}/k_{\text{coll}} \times 100$.

^b Secondary products are indicated as 2° and are listed directly under primary products that produce them.

^c Proton transfer reactions (for the enediyne isomer) are not listed for the *para*-benzynes analog.

^d Reactions with atmospheric H₂O and O₂.

^e Archibold, E. F. Ph.D. Thesis, Purdue University, **2012**.

^f Calculated at either the RHF-BCCD(T)/cc-pVTZ//UB3LYP/cc-pVTZ (biradical singlet state) or RHF-UCCSD(T)/cc-pVTZ//UB3LYP/cc-pVTZ level of theory (all other states).

^g Abs = Abstraction.

^h Percentage of *para*-benzynes analog in the isomer mixture.

Table 2

Reaction Efficiencies^a and Branching Ratios^{b,c} for 5,8-Didehydroisoquinolinium (2), 5-Dehydroisoquinolinium^d (8) and 8-Dehydroisoquinolinium^d (9)
Cations With Several Neutral Reagents

EA _v ^e (eV)	5.32	4.87	5.06
S-T Splitting ^e (kcal/mol)	-3.7	--	--
Addition	38%	I Abs	I Abs
I Abs ^f	26%	Allyl Abs	Allyl Abs
2° I Abs		H Abs	5%
2° Allyl Abs	15%		
2H Abs	14%		
Allyl Abs			
2° Allyl Abs			
Allene Abs	7%		
Efficiency = 0.003% <i>para</i> -benzynes ^g	98%	Efficiency = 35%	Efficiency = 45%
HSCH ₃ Abs	52%	SCH ₃ Abs	SCH ₃ Abs
Addition	21%	H Abs	H Abs
SCH ₃ Abs	15%	e ⁻ Abs	3%
2° SCH ₃ Abs			
2° H Abs	12%		
e ⁻ Abs			
2° SCH ₃ Abs			
SCH ₂ Abs	1%		

	Efficiency = 0.009% <i>para</i> -benzynes ^g 96%	Efficiency = 30%	Efficiency = 36%
Addition	H Abs	H Abs
	H ₂ O Abs	100%	100%
	H Abs	80%	100%
	2° H Abs	16%	100%
	Hydride Abs	6%	100%
Efficiency = 0.002% <i>para</i> -benzynes ^g 93%
H Abs	Efficiency = 10%	More Reactive Isomer 67% Efficiency = 22%
	2° H Abs	H Abs	H Abs
	Addition	100%	100%
	Hydride Abs	82%	100%
	Addition-H	8%	100%
Efficiency = 0.002% (only <i>para</i> -benzynes present)			
		Efficiency = 2%	Efficiency = 4%

^a Reaction efficiencies calculated from least-squares non-linear fits of the pseudo-first order rate plots and are reported as $k_{\text{exp}}/k_{\text{coll}} \times 100$.

^b Secondary products are indicated as 2° and are listed directly under primary products that produce them.

^c Proton transfer reactions (for the enediyne isomer) are not listed for the *para*-benzynes analog.

^d Archibald, E. F. Ph.D. Thesis, Purdue University, **2012**.

^e Calculated at either the RHF-BCCD(T)/cc-pVTZ//UB3LYP/cc-pVTZ (biradical singlet state) or RHF-UCCSD(T)/cc-pVTZ/UB3LYP/cc-pVTZ level of theory (all other states).

^f Abs = Abstraction.

^g Percentage of *para*-benzynes analog in the isomer mixture.