Experimental and Computational Studies on the Formation of Three para-Benzyne Analogues in the Gas Phase

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Abstract: Experimental and computational studies on the formation of three gaseous, positively-charged para-benzyne analogues in a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer are reported. The structures of the cations were examined by isolating them and allowing them to react with various neutral reagents whose reactions with aromatic carboncentered o-type mono- and biradicals are well understood. Cleavage of two iodine-carbon bonds in N-deuterated 1,4-diiodoisoquinolinium cation by collision-activated dissociation (CAD) produced a long-lived cation that showed nonradical reactivity, which was unexpected for a *para*-benzyne. However, the reactivity closely resembles that of an isomeric enediyne, *N*-deuterated 2-ethynylbenzonitrilium cation. A theoretical study on possible rearrangement reactions occurring during CAD revealed that the cation formed upon the first iodine atom loss undergoes ring-opening before the

Keywords: biradicals · distonic ions · ion-molecule reactions · *para*-benzyne · mass spectrometry · ring-opening second iodine atom loss to form an enediyne instead of a *para*-benzyne. Similar results were obtained for the 5,8-didehydroisoquinolinium cation and the 2,5-didehydropyridinium cation. The findings for the 5,8-didehydroisoquinolinium cation are in contradiction with an earlier report on this cation. The cation described in the literature was regenerated by using the literature method and demonstrated to be the isomeric 5,7-didehydro-isoquinolinium cation and not the expected 5,8-isomer.

Introduction

para-Benzyne analogues have been identified as the reactive intermediates of the very potent enediyne antitumor antibiotics (e.g., compound **1**, Scheme 1).^[1] When intercalated into double-stranded DNA, the enediyne component contained within the antitumor antibiotic undergoes a Bergman-type cyclization to form a σ , σ -biradical. Each radical site of the biradical is thought to abstract a hydrogen atom from the sugar–phosphate backbone of each strand of the DNA double helix. The result is an irreversible DNA scission and eventual apoptosis of the cell.^[1]

A few solution studies^[2] conducted on the reaction kinetics of *para*-benzyne and 9,10-didehydroanthracene showed

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Scheme 1. para-Benzyne intermediate (2) formed from calicheamicin (1).

that these biradicals abstract hydrogen atoms at significantly lower rates than analogous monoradicals.^[2a,c] To abstract a hydrogen atom, the nonbonding electrons in these singlet biradicals must partially uncouple in the transition state. This uncoupling results in the loss of stabilizing spin-spin interactions, which raises the transition state energy. This energy increment has been suggested to be directly related to the magnitude of the singlet-triplet splitting (ΔE_{S-T}) of the singlet biradical, or the energy difference between the singlet ground state and the lowest energy triplet state^[2] (other parameters are now known to be important as well^[3]). As ΔE_{S-T} increases in magnitude, radical reactivity decreases, and eventually disappears. For example, due to their large ΔE_{S-T} ortho-benzyne analogues act as activated alkynes and mainly undergo addition-elimination reactions via nonradical mechanisms.^[4] Along with ΔE_{S-T} , the vertical electron affinity (EA) of the radical sites, hydrogen bonding

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ability with the incoming reagent, and the dehydrocarbon atom separation (for *meta*-benzynes only) have been shown to be reactivity-controlling factors for carbon-centered σ , σ -biradicals.^[5]

Despite the obvious importance of σ , σ -biradicals, the difficulty in generating them cleanly, as well as their short lifetimes and high reactivities, make studies of these species in solution quite challenging.^[6] Fortunately, the difficulties associated with condensed-phase studies can be overcome in the gas phase by utilizing the distonic ion approach^[7] in a mass spectrometer. Several studies on the gas-phase reactivities of various σ , σ -biradicals have been published utilizing this method.^[4c,5b,8] However, only one gaseous *para*-benzyne has been reported in the literature,^[8a] and the results presented here cast doubt on whether the species studied was actually a *para*-benzyne.

We report herein thorough experimental and computational studies on three gaseous *para*-benzyne analogues, **4**, **5**, and **6**. To better understand the observed reactions, related monoradicals and isomeric biradicals were also examined.



Results and Discussion

To learn more about the chemical properties of *para*-benzynes, an attempt was made to generate three such species (4, 5, and 6), each containing a positive charge for mass spectrometric manipulation, by cleaving two carbon–iodine bonds in suitable precursors in the gas phase in an FT-ICR mass spectrometer. The structures of the isolated, long-lived ions were examined by allowing them to react with various reagents whose reactions with aromatic carbon-centered σ type mono- and biradicals are well understood (e.g., cyclohexane, tetrahydrofuran, allyl iodide, dimethyl disulfide and, in some cases, *tert*-butyl isocyanide^[9]). The experimental results obtained for each *para*-benzyne are described in detail below.

N-Deutero-1,4-didehydroisoquinolinium cation (4): Cleavage of two carbon-iodine bonds from the precursor, *N*-deutero-1,4-diiodoisoquinolinium cation, was used in an attempt to create the *N*-deuterated 1,4-didehydroisoquinolinium cation (4). The reactivity of the long-lived product ion toward several neutral reagents was examined. With a calculated S-T splitting of $-3.0 \text{ kcal mol}^{-1}$ (BD(T)_{deriv}), the *para*benzyne 4 was expected to react via radical mechanisms like related monoradicals, although more slowly. We first consider the reactivity of the related monoradicals.

Both 4-dehydroisoquinolinium cation (7) and N-deutero-1-dehydroisoquinolinium cation (8) exclusively abstract a thiomethyl (SCH₃) group from dimethyl disulfide and a hydrogen atom from tetrahydrofuran and cyclohexane (Table 1). In addition, they both abstract an iodine atom and an allyl group from allyl iodide. Like other similar monoradicals, the reactivities of **7** and **8** depend upon their electrophilicities, which can be quantified by their (calculated) vertical electron affinities (EA, a measure of the energy released upon attachment of an electron to a radical site). An increase in the vertical EA results in a more polar and more stable transition state, which increases reactivity.^[5c,10] With a calculated EA of 6.50 eV, **8** would be predicted to be more reactive than **7** (EA: 5.79 eV). Indeed, **8** is more reactive than **7** toward all reagents studied. For example, the reaction efficiency of **8** with tetrahydrofuran (83%) is far greater than the reaction efficiency of **7** with the same reagent (39%). This same trend, although not as pronounced, was observed for all of the neutral reagents studied.

Aromatic carbon-centered singlet σ , σ -biradicals with small ΔE_{S-T} react similarly to the monoradicals.^[5b] For example, an isomer of 4, the 4,8-didehydroisoquinolinium cation with a calculated S–T splitting of -3.5 kcal mol⁻¹ $(BD(T)_{deriv})$, mainly undergoes radical reactions but more slowly than related monoradicals. Hydrogen atom abstraction is the main reaction pathway observed for tetrahydrofuran (reaction efficiency: 10%) and cyclohexane (reaction efficiency: 2%). The main reactions observed for allyl iodide are iodine atom abstraction followed by a secondary iodine atom abstraction or an allyl group abstraction (overall reaction efficiency: 41%). Therefore, radical reactions were expected also for the biradical of interest, 4. However, this cation undergoes predominant deuteron and proton transfer to tetrahydrofuran, and predominant addition with dimethyl disulfide (Table 1). In addition, allyl-H abstraction, and allyl abstraction are the main reaction pathways with allyl iodide, and simultaneous abstraction of two hydrogen atoms (or, possibly, a hydride and a proton) was observed with cyclohexane. This reactivity strongly suggests that the structure of the cation generated via homolytic cleavage of the two C-I bonds in the precursor is not 4, as expected. Allyl-H, allyl abstraction and addition have been found to occur via nonradical mechanisms for singlet o,o-biradicals with large S-T splittings (i.e., ortho-benzyne analogues).^[8c,11] Hence, the reactivity of this cation (hereafter referred to as 4') suggests that it is either a biradical with a large S-T splitting or not a biradical at all.

Since *para*-benzynes are known to undergo reversible retro-Bergman rearrangement,^[12] ring-opening of the desired *para*-benzyne analogue **4** to form the unknown cation **4'** was considered as the most likely isomerization process. The calculated (BD(T)_{deriv} barrier (i.e., activation enthalpy) for the formation of one of the two possible enediynes, 2-ethynylbenzonitrilium cation (**9**), is only 3.7 kcalmol⁻¹, while formation of the other enediyne, azacyclodeca-1,5,7-triene-3,9-diyn-1-ylium cation (**10**), has a calculated barrier of 15.4 kcalmol⁻¹ (Figure 1). The lower barrier for formation and the greater stability of **9** (34.0 kcalmol⁻¹ lower in energy than **4** and 37.3 kcalmol⁻¹ lower in energy than **10** (BD(T)_{deriv}); Figure 1) suggest that this enediyne is more likely to be formed than **10**.

Table 1. Reaction efficiencies^[a] and product branching ratios.^[b]

| | Ţ Ţ | ₿ • • • | ↓ ↓ ↓ ↓ ↓ ↓ ↓ |
|--|---|--|---|
| calculated ^[c] S–T splitting [kcalmol ⁻¹] calculated ^[d] electron affinity [eV] | - 5.79 | - 6.50 | -3.0 6.74 |
| \bigcirc | H abs. 100 % efficiency: 18 % | H abs. 100 % efficiency: 37 % | 2×H abs. 100% H/D exchange ^[e] efficiency: 3% |
| $\langle \overset{o}{} \rangle$ | H abs. 100% | H abs. 100% | D ⁺ trans. 62 % H ⁺ trans. 28 % H ₂ O abs. 4 % CH ₂ O abs. 3 % addition 3 % |
| | I abs. 94 % allyl abs. 6 % efficiency: 64 % | I abs. 87 % allyl abs. 13 % | addition 59% allyl-H abs. 21% allyl abs. 20% H/D exchange ^[e] efficiency: 1% |
| ~ ^{\$} ` _{\$} ~ | SCH_3 abs. 100 % efficiency: 71 % | SCH ₃ abs. 100 % efficiency: 87 % | addition 68% e ⁻ abs. 17% (2°) SCH ₃ abs. HSCH ₃ abs. 15% efficiency: 9% |

[a] Reaction efficiency (% of collisions leading to reaction) = $k_{reaction}/k_{collision} \times 100$. [b] abs. = abstraction; trans. = transfer. Secondary products are indicated as (2°) and are listed under the primary products that produce them. [c] Calculated at the [BD(T)/cc-pVDZ–(BD/cc-pVTZ+BD/cc-pVDZ)]//UBPW91/cc-pVDZ level of theory. [d] Calculated at the UB3LYP/aug-cc-pVTZ//UB3LYP/cc-pVTZ level of theory. [e] Some H/D exchange occurs with surfaces of the instrument, but it is not included in the product branching ratios.



Figure 1. Potential energy surface for retro-Bergman rearrangement of 1,4-didehydroisoquinolinium cation (4). Enthalpies (kcalmol⁻¹) calculated at the [BD(T)/cc-pVDZ–(BD/cc-pVTZ+BD/cc-pVDZ)] level of theory.

To test this hypothesis, the *N*-deuterated 2-ethynyl-benzonitrilium cation (9) was generated from a commercially available precursor, 2-ethynylbenzonitrile, and its reactivity was compared to that of the unknown cation 4' (Table 2). The unknown cation and 9 react with dimethyl disulfide via addition (branching ratios 68 and 73%, respectively), electron abstraction (17 and 16%, respectively), and HSCH₃ abstraction (15 and 11%, respectively) with similar branching ratios and identical reaction efficiencies (9%). The similarity in reactivity was also observed for cyclohexane, where the unknown cation and 9 both exclusively abstract two hydrogen atoms (or, possibly, a hydride and a proton) at similar reaction efficiencies (3 and 2%, respectively). The unknown cation and 9 also display similar reaction efficiencies (80 and 88%, respectively) with tetrahydrofuran, but yield somewhat different products with dissimilar branching ratios. The main reaction pathways observed for 9 and the unknown cation are deuteron transfer (branching ratios 62 and 44%, respectively), proton transfer (28 and 52%, respectively), and addition (3 and 3%, respectively). However, unlike 9, the unknown cation 4' also abstracts H_2O (4%) and CH₂O (3%) from tetrahydrofuran, albeit slowly. The discrepancies in reactivity are less pronounced in reactions with allyl iodide and tert-butyl isocyanide, but should be acknowledged. The branching ratios of allyl-H and allyl abstraction from allyl iodide for the unknown cation are 21 and 20%, respectively, while the branching ratios of the two reactions for 9 are 12 and 26%, respectively, with allyl abstraction being the faster reaction pathway. The reaction efficiencies for the unknown cation and 9 with allyl iodide are identical at 1%. The unknown cation and 9 undergo similar reactions (e.g., butyl abstraction, proton transfer, and deuteron transfer) at similar reaction efficiencies (83 and 94%,

Table 2. Reaction efficiencies^[a] and product branching ratios.^[b]

| | $\bigcup_{4}^{\bullet} \sum_{\mathbf{N}}^{\mathbf{N}} \sum_{\mathbf{D}}^{\mathbf{N}}$ | 9 N D | 11 N, H |
|-------------------------|---|--|--------------------|
| \bigcirc | 2xH abs. 100 % H/D exchange ^[c] efficiency: 3 % | 2xH abs. (or H ⁻ abstraction followed by H ⁺ abstraction) 100 % H/D exchange ^[c] efficiency: 2 % | no reaction |
| $\langle \circ \rangle$ | D ⁺ trans. 62 % H ⁺ trans. 28 % H ₂ O abs. 4 % CH ₂ O abs. 3 % | H ⁺ trans. 52 % D ⁺ trans. 44 % | no reaction |
| | addition 3% efficiency: 80% | addition 3 % efficiency: 88 % | |
| | addition 59% allyl-H abs. 21% allyl abs. 20% H/D exchange ^[c] efficiency: 1% | addition 62 % allyl abs. 26 % allyl-H abs. 12 % H/D exchange ^[c] efficiency: 1 % | no reaction |
| _ ^S `S | addition 68% e^- trans. 17% (2°) SCH ₃ abs. HSCH ₃ abs. 15% efficiency: 9% | addition 73 % e ⁻ trans. 16 % (2°) SCH ₃ abs HSCH ₃ abs. 11 % efficiency: 9 % | no reaction |
| NC | H ⁺ trans. and dissoc. 39 % C_4H_8 abs. 24 % addition- C_3H_5D 21 % D ⁺ trans. 16 % H/D exchange ^[c] | C_4H_8 abs. 45 % H ⁺ trans. and dissoc. 32 % addition- C_3H_5D 8 % addition- C_3H_6 8 % D ⁺ trans. 7 % H/D exchange ^[c] | addition 100% |
| | efficiency: 83% | efficiency: 94 % | etticiency: 0.06 % |

[a] Reaction efficiency (% of collisions leading to reaction) = $k_{\text{reaction}}/k_{\text{collision}} \times 100$. [b] abs. = abstraction; trans. = transfer. Secondary products are indicated as (2°) and are listed under the primary products that produce them. [c] Some H/D exchange occurs with surfaces of the instrument, but it is not included in the product branching ratios.

respectively) with *tert*-butyl isocyanide. However, the branching ratios of proton transfer and butyl abstraction are 39 and 24%, respectively, for the unknown cation, whereas the branching ratios of the two reactions for 9 are 32 and 45%, respectively, with butyl abstraction being the faster reaction. While the great similarities in the reactivity between the unknown cation 4' and 9 suggest that the unknown cation population mostly consists of ions with structure 9, the presence of some other minor isomer(s) is also indicated.

To rule out the presence of the second possible ring-opening product, 10, its generation was desired but proved to be difficult. Since deprotonation is the most likely reaction for this cation, the proton affinity (PA) of its conjugate base was calculated (218.6 kcalmol⁻¹; $BD(T)_{deriv}$). Based on this value, 10 should not transfer a proton to tetrahydrofuran $(PA^{[13]} = 196.5 \text{ kcal mol}^{-1})$ or any of the neutral reagents studied (the PAs of dimethyl disulfide, tert-butyl isocyanide and allyl iodide are 194.9,^[13] 208.1,^[13] and 193.4 kcalmol⁻¹, respectively; the latter calculated here at the RHF-RCCSD(T)/6-311G(d,p)//B3LYP/6-311G(d,p)level of theory). This is supported by the experimental observation that the 4-ethynylpyridinium cation (11), which has the same acidic group and is almost of the same size (one carbon less), does not react with most of the neutral reagents studied. An addition product was observed with *tert*butyl isocyanide; however, the reaction is very slow (0.06%; Table 2). In sharp contrast, enediyne **9** (PA = 196.4 kcal mol⁻¹; BD(T)_{deriv}) can transfer a proton to tetrahydrofuran and *tert*-butyl isocyanide. The observation of proton transfer from the unknown cation to these reagents, and the fact that no unreactive component remains, implies that azaenediyne **10** is not formed.

The small inconsistencies observed between the reactivities of the unknown cation 4' and enediyne 9 with allyl iodide and tetrahydrofuran indicate that a small amount of some isomer, in addition to 9, is present. Especially, the observation of slow H₂O and CH₂O abstractions from tetrahydrofuran is interesting. These reactions do not occur for 9. However, *ortho*-benzynes have been observed to undergo facile addition–elimination reactions, including H₂O and CH₂O abstractions from tetrahydrofuran.^[11a] Three isomeric *ortho*-benzyne analogues (**12–14**) were identified as possible rearrangement products of the desired *para*-benzyne analogue 4. The reactivities of these *ortho*-benzyne analogues toward tetrahydrofuran and allyl iodide were examined and compared to the reactivity of 4' (Table 3). Like the unknown cation 4', all three *ortho*-benzynes abstract H₂O and CH₂O

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Table 3. Reaction efficiencies^[a] and product branching ratios.^[b]

| | N ⁺ | 13 × | N 14 |
|--|-----------------------------|----------------------------|----------------------------|
| calculated ^[c] S-T splitting [kcalmol ⁻¹] | $-29.0^{[d]}$ | -25.3 ^[d] | -30.6 ^[e] |
| calculated ^[f] electron affinity [eV] | 6.52 | 6.57 | 5.80 |
| | CH ₂ O abs. 61 % | H ₂ O abs. 43 % | H ₂ O abs. 67% |
| | H_2O abs. 39 % | addition 32% | addition 19% |
| 0 | | CH ₂ O abs. 8% | CH ₂ O abs. 14% |
| $\langle \rangle$ | | H^- abs. 6% | |
| | | H ⁺ transfer 6% | |
| | | 2xH abs. 5% | |
| | efficiency: 88% | efficiency: 95 % | efficiency: 65% |
| | addition 72% | allyl-H abs. 73% | allyl-H abs. 71 % |
| a d | allyl-H abs. 21% | allyl abs. 17% | allyl abs. 18% |
| | allyl abs. 7% | addition 10% | addition 11% |
| | efficiency: 44% | efficiency: 69 % | efficiency: 61% |

[a] Reaction efficiency (% of collisions leading to reaction) = $k_{\text{reaction}}/k_{\text{collision}} \times 100$. [b] abs. = abstraction; secondary products are indicated as (2°) and are listed under the primary products that produce them. [c] Calculated at the RHF-UCCSD(T)/cc-pVTZ//UBPW91/cc-pVDZ level of theory. [d] For this molecule, the lowest energy triplet state has A' symmetry. [e] For this molecule, the lowest energy triplet state has A' symmetry. [e] For this molecule, the lowest energy triplet state has A' symmetry. [f] Calculated at the UB3LYP/aug-cc-pVTZ//UB3LYP/cc-pVTZ level of theory.

from tetrahydrofuran at high efficiencies (49-88%). The ion population 4' and enediyne 9 react with tetrahydrofuran at comparable efficiencies (80 and 88%, respectively). Since the H₂O and CH₂O abstractions occur at a combined efficiency of 7% (H₂O abstraction at 4% and CH₂O abstraction at 3%) for 4', the proportion of the unknown isomer in 4' is estimated to be 3-6%. A significant amount of addition was also observed for the ortho-benzynes 13 and 14. Although a minor addition product was formed for the unknown ion population 4', consideration of the relative branching ratios of the products formed from the enediyne 9 and the unknown ion population 4' suggests that most if not all of the addition product of 4' arises from enediyne 9. ortho-Benzyne analogue 12 is the only ortho-benzyne isomer studied that does not undergo the addition reaction, which supports this isomer as being the additional isomer in the ion population 4'.

The ortho-benzyne analogues react with allyl iodide at substantially greater efficiencies (44–69%) than either 4' or 9 (1% for both; Table 2). If one of these ortho-benzyne isomers is present in the ion population 4' at a level of 3-6%, as estimated above, its reactivity toward allyl iodide should dominate over that of 9. Because the most favorable reaction pathway for 13 and 14 with allyl iodide is allyl-H abstraction, followed by allyl abstraction and addition, while the most favorable reaction pathway for 12 is addition followed by allyl-H abstraction and allyl abstraction, as observed for 4', it appears that the unknown ortho-benzyne analogue in the ion population 4' is 12. This isomer is also calculated to be the most stable among the three ortho-benzyne isomers considered (Figure 2).

The rearrangement of 4 to 9 (and 12) may take place either during the CAD event used to generate 4, after generation due to excess internal energy that 4 gained when formed, or in the ion-molecule complex formed between 4



Figure 2. Relative enthalpies $(kcalmol^{-1})$ of isomeric *ortho*-benzynes calculated at the RHF-UCCSD(T)/cc-pVTZ//UBPW91/cc-pVDZ level of theory.

and a neutral reagent molecule before or during a reaction. To determine when the rearrangement is occurring, Brauman's double well potential energy surface must be considered.^[14] Since these gas-phase ion-molecule reactions occur in a high vacuum environment, the reactions are free from solvent effects, with the exception of the formation of the initial collision complex. Ion-dipole forces between the ion and the molecule lower the potential energy of the collision complex, which, in turn, increases the vibrational and rotational energy of the system. This increase in vibrational and rotational energy can be used to overcome reaction barriers, but not drive endothermic reactions or reactions with a barrier above the energy of the isolated reactants. Reaction rates are controlled by the difference in energy between the reactants and the transition state. The retro-Bergman rearrangement barrier for 4 (3.7 kcalmol⁻¹; Figure 1) to form 9 is low enough to be overcome in many collision complexes,^[15] but possibly not in the complex with cyclohexane. Since cyclohexane is nonpolar and does not have a dipole, the solvation energy it provides is very small compared to the other reagents studied. If para-benzyne 4 were to retain its structure before collision with cyclohexane, it should not rearrange in the complex with cyclohexane, but react by hy-

drogen atom abstraction. Indeed, two hydrogen atom abstractions (or, possibly, a hydride and a proton abstraction) were observed. However, two hydrogen atom abstractions (likely a hydride and a proton) were also observed for enedivne 9 and at the same efficiency as for 4', suggesting that 4 has already isomerized to 9 before the collision complex is formed.

To gain further insight on how 9 and 12 might be formed during the (attempted) generation of 4 by using CAD, the C-I homolytic bond dissociation energies for the precursor of 4, the 1,4-diiodoisoquinolinium cation, were calculated at the (U)B3LYP/6-311G(d,p)//(U)B3LYP/6-311G(d,p) level of theory to be 66.1 kcalmol⁻¹ for the C-1 position and 65.4 kcalmol⁻¹ for the C-4 position. Based on the similarity of these values, either C-I bond can cleave during the first SORI-CAD event to form two isomeric monoradicals. The lowest energy reaction pathway for both monoradicals is the formation of 23 via ring-opening followed by iodine atom loss (for the 4-dehydro-1-iodo isomer, see Figure 3; the highest energy barriers for the 4-dehydro-1-iodo and 1-dehydro-4-iodo isomers are calculated to be 44.8 and 47.8 kcalmol⁻¹, respectively, not shown). Direct iodine atom loss would require a lot more energy (63.5 for the 4-dehydro isomer and 62.8 for the 1-dehydro isomer, not shown). Formation of *ortho*-benzyne **12** requires about 10 kcalmol⁻¹ more energy than formation of 23 for the 4-dehydro isomer (Figure 3), which explains why only a small amount of this cation was observed. A mechanism for the formation of 12 that is in agreement with our calculations (Figure 3) and deuterium labeling experiments is proposed in Scheme 2. ortho-Benzyne 14 cannot be formed from the 1-dehydro isomer since this would require even more energy than the direct iodine atom cleavage ($86.1 \text{ kcal mol}^{-1}$). This is in agreement with our experimental results indicating that 14 is not generated.

One experimental detail still needs to be delineated. While the unknown cation population 4' and the enediyne 9





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show similar reactivity, suggesting that most of the ions in the unknown ion population have the structure 9 and not 4, the extent of proton and deuteron transfer to tetrahydrofuran is significantly different (Table 2). The enediyne generated upon ring-opening of the desired *para*-benzyne (Figure 1) carries a deuterium on the nitrogen atom (this is where the deuterium was placed upon ionization of the precursor, 1,4diiodoisoquinoline). Hence, 4' is expected, and was observed, to mostly transfer a deuteron to tetrahydrofuran. In sharp contrast, the authentic (deuterated) enedivne 9 transfers roughly an equal amount of protons and deuterons to tetrahydrofuran. To understand why this is occurring, the proton affinities at each heavy atom of the conjugate base of 9 were calculated (Figure 4). As expected, the aromatic carbon atoms are not optimal sites for protonation. Interestingly, the proton affinities of the two most basic sites, the terminal carbon atom of the alkyne group and the nitrogen atom of the nitrile group, are similar (188.2 and. 195.4 kcal mol⁻¹, respectively). Based on these calculations, the ob-

served transfer of both a proton and a deuteron from 9 to tetrahydrofuran is not surprising. When the conjugate base of 9 (24) is ionized by deuteron transfer, it is likely to be deuterated at both the nitrile and the terminal alkyne functionalities. When deuteration occurs at the nitrile group, only a deuteron will be available for transfer to tetrahydrofuran. However, when deuteration occurs at the ethynyl group, the proton already present at the terminal carbon atom of the alkyne group and the added deuteron are both available for transfer to tetrahydrofuran (Scheme 3).

Figure 3. Potential energy surface for the formation of 4, 12, and 23 from 1-iodo-4-dehydroisoquinolinium cation (15). Enthalpies (kcalmol⁻¹) calculated at the (U)B3LYP/6-311G(d,p)//(U)B3LYP/6-311G(d,p) level of theory.

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$$(164.0) (168.5) (188.2) (164.0) (156.3) (156.3) (169.7) (161.8) (164.8) N (195.4)$$

Figure 4. Calculated (G3MP2B3) proton affinities (kcalmol $^{-1}$) at each heavy atom of the conjugate base of **9**.



Scheme 3. Proposed sites for deuteration of 24.

The branching ratios for proton transfer (52%) and deuteron transfer (44%; Table 2) observed for deuterated enediyne **24** suggest that both the alkyne group and nitrile group are deuterated, but the alkyne group with a significant preference for an as yet unknown reason. Finally, the observation of some proton transfer for **4'** is likely a result of an intermolecular transfer (facilitated by tetrahydrofuran) of the deuteron from the nitrogen atom of the nitrile group to the terminal carbon atom of the alkyne group. After transfer to the alkyne group, both a proton and a deuteron are available for transfer to tetrahydrofuran.

5,8-Didehydroisoquinolinium cation (5): The 5,8-didehydroisoquinolinium cation has been studied previously, and was found to undergo radical reactions, albeit very slowly.[8a] However, the finding of a facile ring-opening for the 1,4diiodoisoquinolinium cation after iodine atom loss warranted a re-examination of 5. To control the site of the first cleavage, a different precursor (protonated 5-iodo-8-nitroisoquinoline, instead of protonated 5,8-dinitroisoquinoline) was used to generate 5. The nitro group in the new precursor cation cleaves first, yielding the 8-dehydro-5-iodoisoquinolinium cation as the intermediate. When this cation was subjected to SORI-CAD, a cation believed to be 5 was generated. Surprisingly, after the cation was isolated, it was found to be completely unreactive toward tetrahydrofuran, allyl iodide, cyclohexane, and dimethyl disulfide. Very slow addition to tert-butyl isocyanide and HCN abstraction from this reagent were observed. This reactivity is drastically different from what was expected, since the related monoradicals, the 5- (26) and 8-dehydroisoquinolinium cations (27), show typical radical reactivity (Table 4; monoradical 27 is more reactive than 26 due to its greater (calculated) EA; 27: 5.25 eV; 26: 5.08 eV). This reactivity is also distinctly different from that reported for this molecule in the earlier study.^[8a] Hence, the new long-lived cation generated upon loss of a nitro group and an iodine atom from 5-iodo-8-nitroisoquinolinium cation is concluded not to be 5, and it will be referred to as 5' hereafter.

A retro-Bergman rearrangement immediately after the formation of **5** from the new precursor might explain the

| | * * * * * * * * * * * | 27 N H | 5 5 |
|--|---|--|--|
| calculated ^[c] S–T splitting [kcalmol ⁻¹] calculated ^[d] electron affinity [eV] | - 5.08 | - 5.25 | -2.4 5.61 |
| \bigcirc | H abs. 100% efficiency: 3% | H abs. 100 % efficiency: 3 % | no reaction |
| \diamond | H abs. 100 % efficiency: 8 % | H abs. 100 % efficiency: 25 % | no reaction |
| | I abs. 98 % allyl abs. 2 % efficiency: 36 % | I abs. 100 % efficiency: 43 % | no reaction |
| ^S `_S_ | SCH_3 abs. 100 % efficiency: 33 % | SCH ₃ abs. 100 % efficiency: 34 % | no reaction |
| NC | CN abs. 94 % HCN abs. 6 % efficiency: 63 % | CN abs. 100 % efficiency: 68 % | addition 93 % HCN abs. 7 % efficiency: 0.3 % |

Table 4. Reaction efficiencies^[a] and product branching ratios.^[b]

[a] Reaction efficiency (% of collisions leading to reaction) = $k_{reaction}/k_{collision} \times 100$. [b] abs. = abstraction; trans. = transfer. Secondary products are indicated as (2°) and are listed under the primary products that produce them. [c] Calculated at the [BD(T)/cc-pVDZ-(BD/cc-pVTZ+BD/cc-pVDZ)]//UBPW91/ cc-pVDZ level of theory. [d] Calculated at the UB3LYP/aug-cc-pVTZ//UB3LYP/cc-pVTZ level of theory

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unexpected reactivity. However, this biradical cannot form an acidic enediyne (like 9, a protonated nitrile, discussed above) because the biradical moiety is in the benzene ring, not the pyridine ring. Instead, an enediyne with the acidic proton on the pyridine nitrogen (much less acidic than a protonated nitrile) can be formed (33; Scheme 4). The



Scheme 4. Proposed mechanism for the formation of **33** from **29**. Relative enthalpies (kcalmol⁻¹) are shown below each structure and were calculated at the (U)B3LYP/6-311G(d,p)//(U)B3LYP/6-311G(d,p) level of theory.

chemical properties of a similar enediyne, **11**, were discussed above (Table 2). Enediyne **11** showed no reactivity towards tetrahydrofuran, allyl iodide, cyclohexane, or dimethyl disulfide, and slow addition was observed for *tert*-butyl isocyanide (Table 2). These findings are consistent with the hypothesis that **5**' actually has the structure **33**.

To further explore the process used to generate **5**, the monoradical (**29**) formed by cleaving the nitro group from 5-iodo-8-nitroisoquinolinium cation (**28**) was isolated and allowed to react with tetrahydrofuran (Scheme 5). Monoradical **29** reacts exactly like monoradical **27**: only hydrogen



Scheme 5. Generation of 29 and its reactivity toward tetrahydrofuran.

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atom abstraction was observed at the same efficiency (25%; Table 4). Thus, it appears unlikely that any rearrangement takes place during the first CAD event.

The above findings suggest that ring-opening required to form **33** takes place either during or after the second CAD. At the BD(T)_{deriv} level of theory, the calculated activation enthalpy for retro-Bergman rearrangement of **5** via cleavage of the C6–C7 bond is 10.0 kcalmol⁻¹ (that for cleavage of the C4a–C8a bond is 15.9 kcalmol⁻¹). Considering that the solvation energies for gas-phase ion–molecule complexes are typically 5–20 kcalmol⁻¹,^[15] and that they are lowest for hydrocarbons with no permanent dipole moment, one can assume that if **5** had retained its structure prior to collision with cyclohexane, hydrogen atom abstraction (instead of rearrangement) should be observed. However, no reaction was observed, further supporting the hypothesis that **5** had already rearranged before this collision.

To determine whether ring-opening during the second CAD event occurs before or after the loss of the iodine atom, several possible pathways were examined computationally. The results indicate that ring-opening of **29** via the process shown in Scheme 4 requires substantially less energy than the loss of the iodine atom.

The final issue that needs to be addressed is why **5**' was found to behave so differently than that observed in the earlier study.^[8a] Therefore, the dinitro precursor used in the earlier study to generate **5** was resynthesized by using the same published protocol.^[16] Surprisingly, based on X-ray characterization of the product (see the Supporting Information), this synthesis yields 5,7-dinitro-isoquinoline instead of 5,8dinitroisoquinoline. Hence, the biradical examined in the earlier study^[8a] was not **5** or **5'** but the isomeric 5,7-didehydroisoquinolinium cation.

2,5-Didehydropyridinium cation (6): To generate the parabenzyne analogue 6, two consecutive SORI-CAD events were applied to the 2,5-diiodopyridinium cation to cleave the two carbon-iodine bonds. The product cation (6') was isolated and allowed to react with several neutral reagents. The dominating reaction was proton transfer, a nonradical reaction, which was not observed for the related monoradicals, 2-dehydropyridinium cation (34) and 3-dehydropyridinium cation (35) (Table 5). The proton affinities (PA) for tetrahydrofuran, dimethyl disulfide, tert-butyl isocyanide, and allyl iodide are 196.5,^[13] 194.9,^[13] 208.1,^[13] and 193.4 kcal mol⁻¹, respectively (the last calculated here at the RHF-RCCSD(T)/6-311G(d,p)//B3LYP/6-311G(d,p) level of theory). The PA of 2,5-didehydropyridine (the conjugate base of 6) is calculated to be $200.1 \text{ kcal mol}^{-1}$ (RHF-BCCD(T)/cc-pVTZ//UBPW91/cc-pVDZ). Hence, proton transfer from 6 to tert-butyl isocyanide is exothermic, but it is endothermic for all of the other neutral reagents. However, proton transfer to all of the neutral reagents occurs quite rapidly (Table 5), and this suggests that the long-lived ion generated in the above experiment (6') does not have structure 6.

Table 5. Reaction efficiencies^[a] and product branching ratios.^[b]

| | N + − H | • [] | • () + - H + H |
|---|---|--|---|
| | 34 | 35 | 6 |
| calculated ^[c] S–T splitting [kcalmol ⁻¹] calculated electron affinity [eV] | – 6.69 ^[d] | - 6.13 ^[d] | -4.9 7.03 ^[d] |
| $\langle \circ \rangle$ | H abs. 100 % efficiency: 76 % | H abs. 100 % efficiency: 38 % | H ⁺ trans. 100 % efficiency: 99 % |
| | I abs. 84% Allyl abs. 16% efficiency: 69% | I abs. 90 % Allyl abs. 10 % efficiency: 57 % | $\mathrm{H^{+}}$ trans. 100 % efficiency: 31 % |
| _ ^S `S´ | SCH ₃ abs. 100 % H abs. 5 % SSCH ₃ abs. 1 % efficiency: 79 % | SCH_3 abs. 100 % efficiency: 77 % | H ⁺ trans. 100 % efficiency: 96 % |
| | CN abs. 94 % HCN abs. 6 % efficiency: 93 % | CN abs. 96 % HCN abs. 4 % efficiency: 87 % | ${ m H^+}$ trans. and dissociation 76% ${ m C_4H_8}$ abs. 24% efficiency: 99% |

[a] Reaction efficiency (% of collisions leading to reaction) = $k_{\text{reaction}}/k_{\text{collision}} \times 100$. [b] abs. = abstraction; trans. = transfer. Secondary products are indicated as (2°) and are listed under the primary products that produce them. [c] Calculated at the BD(T)/cc-pVTZ//UBPW91/cc-pVDZ level of theory. [d] Calculated at the UB3LYP/aug-cc-pVTZ//UB3LYP/cc-pVTZ level of theory.

Two possible isomeric enediynes (**39** and **40**) can be generated upon retro-Bergman rearrangement of **6** (paths a and b; Scheme 6). The lowest-energy barrier (to form **39**) is 8.3 kcalmol⁻¹ (path a; Scheme 6; BD(T)/BS-III), which is lower by 12.5 kcalmol⁻¹ than the ring-opening barrier to form **40** (path b; Scheme 6). These results suggest that enediyne **39** may be formed from **6**. To further explore which enediyne was formed in the experiments discussed above, the proton affinities of the conjugate bases of the two enediynes, **36** and **37**, were computed (190.7 and 204.6 kcalmol⁻¹, respectively; RHF-UCCSD(T)/cc-pVTZ//UBPW91/



Scheme 6. Possible ring-opening pathways for 6.

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theory.

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cc-pVDZ). The calculated proton affinities show that **40** cannot transfer a proton to tetrahydrofuran, dimethyl disulfide, or allyl iodide, since all these reactions are endothermic and that only **39** can transfer a proton to these neutral reagents.

To explore whether enediyne **39** is formed upon ringopening of **6** or before formation of **6**, computational studies were carried out to explore the various possible processes occurring upon CAD after cleavage of the first iodine atom from 2,6-diiodopyridinium cation. The two carbon–iodine bonds have similar strengths (position 2: 69.1 kcalmol⁻¹; position 5: 67.4 kcalmol⁻¹) and hence, both are probably cleaved. The computational results suggest that again, ringopening of the monoradicals generated upon the first iodine atom loss is a lower energy process than loss of the remaining iodine atom to generate **6** (for the 2-monoradical, see Scheme 7).



enthalpies (kcalmol⁻¹) are shown below each structure and were calculat-

ed at the (U)B3LYP/6-311G(d,p)//(U)B3LYP/6-311G(d,p) level of

Conclusion

The generation of three positively-charged para-benzyne analogues was attempted by two CAD events of appropriate precursor cations in an FT-ICR mass spectrometer. When the reactivities of the isolated, long-lived cations were compared to those of analogous monoradicals and isomeric biradicals, none of these cations behaved like para-benzyne analogues. The experimental and quantum chemical findings indicate that upon CAD of the monoradical precursors, ring-opening rather than iodine atom cleavage occurred, yielding an enediyne rather than the para-benzyne. While two possible enediyne isomers exist for each para-benzyne analogue, only the more stable one was formed for two of them. The generation of one of the para-benzyne analogues, the 1,4-didehydroisoquinolinium cation, is further complicated by the competing formation of an isomeric ortho-benzyne analogue, the 2-dehydroisoquinolinium radical cation, via a rearrangement reaction.

Finally, a previously reported^[8a] para-benzyne analogue, the 5,8-didehydroisoquinolinium cation **5**, was reexamined since it displayed different reactivity from that observed here. The synthetic route^[16] utilized in the literature report^[8a] for the para-benzyne precursor, 5,8-diiodoisoquinoline, was found not to produce a para-benzyne but instead a *meta*-benzyne precursor, the isomeric 5,7-diiodoisoquinoline. Upon protonation and two CAD events, this precursor yields the 5,7-didehydroisoquinolinium cation that undergoes very slow radical reactions.^[8a]

Experimental Section

Cyclohexane, tetrahydrofuran, allyl iodide, dimethyl disulfide and tert-butylisocyanide were purchased from Sigma-Aldrich and used as received. The precursors for 4, 9, 14, 34, and 35, namely, 1,4-diiodoisoquinoline (Ubichem PLC), 2-ethynylbenzonitrile (Apollo Scientific, Ltd.), 4-bromoisoquinoline (Sigma-Aldrich), 2-iodopyridine (Sigma-Aldrich), and 3iodopyridine (Sigma-Aldrich), respectively, were obtained commercially and used as received. The precursors for 7, 8, 11, 12, and 13, namely, 4-iodoiso-quinoline, 1-iodoisoquinoline, 4-ethynylpyridine, 1-iodoisoquinoline and 3-iodoisoqui-noline, respectively, were synthesized using literature methods.^[17] Similarly, the precursors for 5 and 26, 5-iodo-8-nitroisoquinoline and 5-iodoisoquinoline, respectively, were synthesized using literature procedures.^[17c] Alkyne 11 was generated from commercial 4-ethynylpyridine (TCI America) and 6 from 2,5-diiodopyridine (Sigma-Aldrich). 8-Iodoisoquinoline (precursor for 27) was synthesized as described below. A mixture of 8-aminoisoquinoline (0.48 g, 3.36 mmol) (Carbocore), concentrated HCl (3 mL), and H2O (3 mL) was cooled in an ice-salt bath to -5°C. After cooling, a solution of NaNO2 (0.28 g, 4.03 mmol) in H2O (2 mL) was added dropwise to give a red solution. The solution was stirred for 15 min, and a solution of KI (1.12 g, 6.73 mmol) in H₂O (3 mL) was added. The mixture was then heated for 3 h at 100 °C, cooled, and basified with aqueous NH₃. The reaction mixture was extracted with dichloromethane and the organic layer was washed with 5% sodium metabisulfite followed by brine solution. The organic layer was dried with sodium sulfate. The product was isolated (0.52 g, 60 %) by using column chromatography (silica gel; CH2Cl2/MeOH=95:5). ¹H NMR (400 MHz, CDCl3): $\delta = 7.30$ (t, J = 7.9 Hz, 1 H), 7.44 (d, J = 5.6 Hz, 1 H), 7.71 (d, J =7.1 Hz, 1H), 8.05 (d, J=7.7 Hz, 1H), 8.54 (d, J=5.7 Hz, 1H), 9.35 ppm (s, 1 H); ¹³C NMR (400 MHz, CDCl3): $\delta = 97.8$, 119.9, 127.4, 128.7, 131.1, 136.9, 138.7, 143.9, 156.6 ppm; ESI-MS: *m*/*z*: 256 [*M*+H]⁺.

All experiments were performed in a previously described^[8b] 3-T Finnigan FTMS 2001 dual-cell Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR). A proton or a deuteron was attached to the radical precursors by using self-chemical ionization, or methanol or $[D_6]$ acetone (Sigma–Aldrich) chemical ionization. Deuteration prevents isobaric contamination of the protonated precursor by the ¹³C isotope of the molecular ion, which would have the same m/z value as the protonated precursor. This method was used only when a significant amount of precursor molecular ions, along with the protonated precursors, was present.

The protonated (or deuterated) precursors were isolated and transferred from one cell into the other cell. Radical sites were generated via sustained off-resonance irradiation collision-activated dissociation^[18] (SORI-CAD) and the resulting radicals were cooled for one second by allowing IR emission and collisions with argon gas. The cations were then isolated using previously published methods.^[4c,19] All cations were allowed to react with neutral reagents for variable periods of time.^[4c,8a,b,19] The second-order reaction rate constants ($k_{reaction}$) were measured, and the reaction efficiencies (($k_{reaction}/k_{collsion}$)×100%) were determined using previously described methods.^[9a,19,20] While the accuracy of the efficiency measurements is estimated to be less than +10%.

Geometries for all species were computed by using density functional theory (DFT) with either the correlation-consistent polarized valencedouble- ζ (cc-pVDZ^[21]) basis set, the correlation-consistent polarized valence-triple- ζ (cc-pVTZ^[21]) basis set or the 6-311G(d,p)^[22] basis set. Hereafter, these basis sets will be referred to as BS-I, BS-II, and BS-III, respectively. These DFT calculations use the gradient-corrected exchange functional of Becke,^[23] which is combined with either the gradient-corrected correlation functional of Lee, Yang and Parr^[24] (B3LYP) or that of Perdew et al.^[25] (BPW91). All DFT geometries were verified to be local minima by computation of analytic vibrational frequencies, and these (unscaled) frequencies were used to compute zero-point vibrational energies (ZPVE) and 298 K thermal contributions $(H_{298}-E_0)$ for all species. DFT calculations for doublet states of monoradicals, and triplet states of biradicals, employed an unrestricted formalism. Total spin expectation values for Slater determinants formed from the optimized Kohn-Sham orbitals did not exceed 0.77 (with the exception of 26: 0.88) and 2.02 for doublet and triplet states, respectively. For singlet biradicals, the DFT "wave function" was allowed to break spin symmetry by using an unrestricted formalism.^[26] Total spin expectation values for Slater determinants formed from the optimized Kohn-Sham orbitals in these cases ranged widely between 0.0 and 1.0. Geometry optimization using the unrestricted formalism has been shown to give more accurate geometries for a number of relevant aromatic biradicals.^[26,27]

To compute vertical electron affinities for the charged aryl radicals, single-point calculations (B3LYP/aug-cc-pVTZ37) using the B3LYP/BS-II optimized geometry for each monoradical or biradical were also carried out for the states that are produced when a single electron is added to the nonbonding σ orbital (or one of the two such orbitals) of each molecule.^[28] Thus, for the monoradicals (doublet ground states), these calculations were carried out for (zwitterionic) singlet states, whereas (zwitterionic) doublet states were computed for each of the biradicals (singlet initial states).^[29] The vertical electron affinities of the charged aryl radicals were computed as either [E_0 (monoradical; doublet state)]–[E_0 (monoradical+electron; singlet state)] or [E_0 (biradical; singlet state)]–[E_0 (biradical+electron; doublet state)]. Note that because these are vertical electron affinities, zero-point vibrational energies (ZPVEs) and 298 K thermal contributions to the enthalpy are not included.

Coupled-cluster calculations for single-configuration reference wave functions expanded in Brueckner^[30] (BD(T)) orbitals were carried out for some of the species by using BS-II and including all single and double excitations and a perturbative estimate for triple excitations. Brueckner orbitals eliminate contributions from single excitations in the coupled-cluster ansatz, and this alleviates instabilities^[31] associated with very large singles amplitudes in the more common CCSD(T) method that have previously been observed for aromatic biradicals having low degrees of symmetry.^[26c] The BD(T) calculations were of the single-point variety and

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were carried out by using the BPW91/BS-I optimized geometries. In addition, two types of BD(T) calculations were performed for the molecules studied here: 1) "direct" BD(T)/BS-II, and 2) "derived" BD(T)/BS-II. The latter method (hereafter referred to as "BD(T)deriv") was used for many of the larger molecules and involves the following single-point calculations: BD(T)/BS-I, BD/BS-II and BD/BS-I. By using these three single-point energies, a "derived" BD(T)/BS-II energy is obtained as: [BD(T)/BS-I-(BD/BS-II+BD/BS-I)]. All BD(T) calculations employed a restricted Hartree-Fock (RHF) reference for closed-shell molecules and an unrestricted Hartree-Fock (UHF) reference for open-shell molecules. Finally, in a few cases, coupled-cluster calculations were performed at either the RHF-(U)CCSD(T)/BS-II//UBPW91/BS-I or the RHF-BCCD(T)/BS-II//UBPW91/BS-I level of theory. For the former calculations, the T1 diagnostic did not exceed 0.023.

Molecular orbital calculations were carried out with the Gaussian $03^{[32]}$ and Molpro^[33] electronic structure program suites.

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