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# Polar Effects Control the Gas-Phase Reactivity of *para*-Benzyne Analogs

Huaming Sheng,<sup>[a]</sup> Xin Ma,<sup>[a]</sup> Hao-Ran Lei,<sup>[a]</sup> Jacob Milton,<sup>[a]</sup> Weijuan Tang,<sup>[a]</sup> Chunfen Jin,<sup>[a]</sup> Jinshan Gao,<sup>[a]</sup> Ashley M. Wittrig,<sup>[a]</sup> Enada F. Archibold,<sup>[a]</sup> John J. Nash,<sup>[a]</sup> and Hilikka I. Kenttämäa\*<sup>[a]</sup>

We report herein a gas-phase reactivity study on a *para*-benzyne cation and its three cyano-substituted, isomeric derivatives performed using a dual-linear quadrupole ion trap mass spectrometer. All four biradicals were found to undergo primary and secondary radical reactions analogous to those observed for the related monoradicals, indicating the presence of two reactive radical sites. The reactivity of all biradicals is substantially lower than that of the related monoradicals, as expected based on the singlet ground states of the biradicals. The cyano-substituted biradicals show substantially greater reactivity than the analogous unsubstituted biradical. The greater reactivity is rationalized by the substantially greater (calculated) electron affinity of the radical sites of the cyano-substituted biradicals, which results in stabilization of their transition states through polar effects. This finding is in contrast to the long-standing thinking that the magnitude of the singlet-triplet splitting controls the reactivity of *para*-benzyne.

*para*-Benzyne and its analogs have received considerable attention since some *para*-benzyne analogs were reported to act as the biological “warhead” of enediyne natural products (e.g. calicheamicins, esperamicins and dynemicins) that show high antitumor activity.<sup>[1–4]</sup> The enediyne unit can undergo Bergman-cyclization in vivo to form a highly reactive *para*-benzyne intermediate that can irreversibly cleave double-stranded DNA through hydrogen atom abstraction from each DNA strand, ultimately leading to cell apoptosis.<sup>[1–4]</sup> Unfortunately, these enediyne natural products are highly toxic and therefore have seen only limited use in cancer treatment.<sup>[5]</sup>

Better understanding of the fundamental chemical properties of *para*-benzyne analogs may facilitate the design of less toxic synthetic drugs. *para*-Benzyne has been measured to have a singlet–triplet (S–T) splitting of  $-3.8 \text{ kcal mol}^{-1}$  and therefore a singlet ground state.<sup>[6]</sup> The low reactivity of two pyridine-based *para*-benzyne analogs compared to related monoradicals in solution has been suggested to be a result of the coupling

between the two unpaired electrons.<sup>[7]</sup> It has been proposed that the two radical sites must partially uncouple in the transition states of radical reactions, which increases the transition state energy.<sup>[8]</sup> Accordingly, the larger the value magnitude of the S–T splitting, the lower is the reactivity expected to be.<sup>[7,8]</sup>

Attaching a charged moiety to a reaction intermediate of interest (the “distonic ion approach”<sup>[9–13]</sup>) has been successfully utilized to characterize the gas-phase reactivity of several *meta*-benzyne analogs in mass spectrometers. In a recent study,<sup>[14]</sup> two *para*-benzyne analogs with different skeletons, the 5,8-didehydroisoquinolinium cation and the 2,5-didehydropyridinium cation (**1**, Figure 1), were successfully generated in a dual-linear quadru-

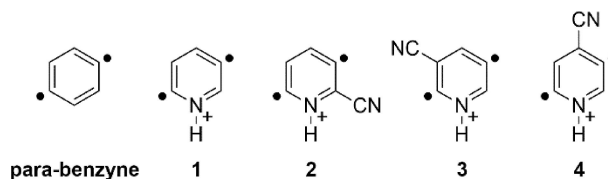


Figure 1. *para*-Benzyne analogs studied.

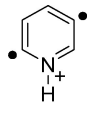
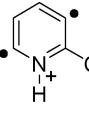
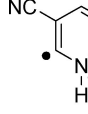
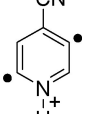
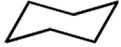
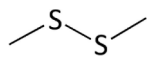
pole ion trap mass spectrometer<sup>[15]</sup> and their gas-phase reactivity toward several reagents was studied. The more polar biradical **1** (with the greater calculated vertical electron affinity ( $EA_v$ ) of the radical sites; 6.76 vs. 5.32 eV; calculated at the RHF-BCCD(T)/cc-pVTZ//UB3LYP/cc-pVTZ level of theory) was found to be more reactive, in spite of its greater S–T splitting ( $-4.6$  vs.  $-3.7 \text{ kcal mol}^{-1}$ , same level of theory). This preliminary result suggests that  $EA_v$  is an important reactivity-controlling parameter for polar *para*-benzyne analogs. In order to further explore this issue, we have studied the gas-phase reactivity of three isomeric *para*-benzyne analogs with the pyridinium skeleton; namely, the three cyano-substituted 2,4-didehydropyridinium cations **2–4** (Figure 1), and compared their reactivity to that of their unsubstituted analog (**1**, Figure 1).

The reactivity results obtained for **1–4** upon interactions with cyclohexane and dimethyl disulfide are shown in Table 1. To better understand the observations made for these *para*-benzyne analogs, their reactivities are compared to those of related 2-dehydro-pyridinium cations (if this word is not split in the final publication, remove the hyphen cations with no cyano-group (**11**) or a cyano-group at the 2-, 3- or 6-position (**5**, **7** and **9**) and related 3-dehydropyridinium cations with no cyano-

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**Table 1.** Reaction efficiencies<sup>[a]</sup> (eff.) and product branching ratios<sup>[b,c]</sup> for reactions of biradicals put these numbers in bold > 1–4<sup>[d]</sup> with cyclohexane and dimethyl disulfide, and their calculated<sup>[d]</sup> vertical electron affinities (EA<sub>v</sub>) and S–T splittings (ΔE<sub>S–T</sub>), as well as the proton affinities (PA) of their conjugate bases.

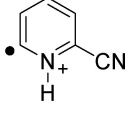
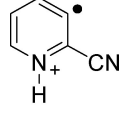
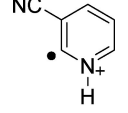
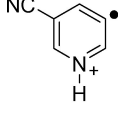
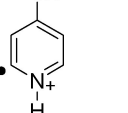
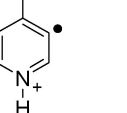
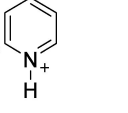
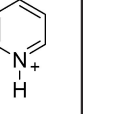
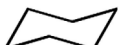
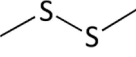
				
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
EA <sub>v</sub> [eV]	6.65	7.25	7.39	7.26
ΔE <sub>S–T</sub> [kcal mol <sup>-1</sup> ]	-5.3	-4.8	-4.5	-4.2
PA [kcal mol <sup>-1</sup> ]	198.9	185.6	185.5	187.3
	H abs, e-transfer 52% 2xH abs 48% H abs, addition 1%	H abs, e-transfer 46% 2xH abs 45% H abs, addition 9%	H abs, e-transfer 48% 2xH abs 42% H abs, addition 10%	2xH abs 66% H-abs, e-transfer 18% H abs, addition 16%
PA <sup>[f]</sup> = 164.2 kcal mol <sup>-1</sup>	eff. = 0.1%	eff. = 2%	eff. = 1%	eff. = 1%
	SCH <sub>3</sub> abs 40% 2° SCH <sub>3</sub> abs HSCH <sub>3</sub> abs 34% e <sup>-</sup> abs 14% SCH <sub>3</sub> abs 7% SSCH <sub>3</sub> abs 5% 2° SCH <sub>3</sub> abs	H <sup>+</sup> transfer 96% 2° addition – CH <sub>3</sub> SH SCH <sub>3</sub> abs 2% 2° SCH <sub>3</sub> abs HSCH <sub>3</sub> abs 1% e <sup>-</sup> Abs 1% SSCH <sub>3</sub> abs trace 2° SCH <sub>3</sub> abs	H <sup>+</sup> transfer 62% 2° addition – CH <sub>3</sub> SH SCH <sub>3</sub> abs 33% 2° SCH <sub>3</sub> abs HSCH <sub>3</sub> abs 2% SSCH <sub>3</sub> abs 2% e <sup>-</sup> Abs 1% 2° SCH <sub>3</sub> abs	SCH <sub>3</sub> abs 47% 2° SCH <sub>3</sub> abs H <sup>+</sup> transfer 43% 2° addition – CH <sub>3</sub> SH SSCH <sub>3</sub> abs 5% HSCH <sub>3</sub> abs 4% e <sup>-</sup> Abs 1% 2° SCH <sub>3</sub> abs
PA <sup>[f]</sup> = 194.9 kcal mol <sup>-1</sup>	eff. = 0.8%	eff. = 55%	eff. = 55%	eff. = 41%

[a] Reaction efficiency (eff.; % of collisions leading to reaction) =  $k_{\text{reaction}}/k_{\text{collision}} \times 100$ ; precision this underline is way too thick in the pdf version > ±10%; accuracy same here > ±50%. < or use the same style as in Table 2 [b] abs = abstraction. [c] Secondary products are listed below the primary product that produced them and indicated by 2°. [d] Experimental data for **1** taken from ref. 14. [e] All values calculated at the CASPT2/CASSCF(m,n)/cc-pVTZ//CASSCF(m,n)/cc-pVTZ level of theory. Singlet–triplet splittings and proton affinities corrected to 298 K by using the (unscaled) UB3LYP/cc-pVTZ frequencies. Proton affinities calculated by using an isodesmic reaction involving proton transfer to pyridine. [f] Experimental value from ref. 19.

group (**12**) or a cyano-group at the 1-, 4- or 5-position (**6**, **8** and **10**; Table 2). All monoradicals exclusively abstract a H atom from cyclohexane and a SCH<sub>3</sub> group from dimethyl disulfide, as expected.<sup>[16]</sup> The monoradicals with the radical site at the 2 position (C-2) are more reactive than those with the radical site at the 3-position (cyclohexane: 46–89% vs. 20–50%; dimethyl disulfide: 90–100% vs. 83–90%, respectively; Table 2). This can

be explained by the differences in their electrophilicities, quantified here by their (calculated) EA<sub>v</sub> values. The greater the EA<sub>v</sub>, the more polar the transition state, and the lower its energy.<sup>[17]</sup> Previous calculations suggest that the EA<sub>v</sub> of analogous monoradicals with the radical site at the 2-position is larger than for radicals with the radical site at the 3-position,<sup>[17]</sup> thus leading to greater reactivity.<sup>[14]</sup> The cyano-substituent

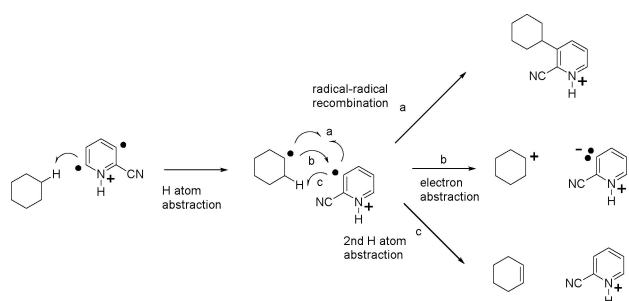
**Table 2.** Reaction efficiencies<sup>[a]</sup> (eff.) and product branching ratios<sup>[b]</sup> for reactions of monoradicals put these numbers in bold > 5–10<sup>[c]</sup> with cyclohexane and dimethyl disulfide and their calculated<sup>[d]</sup> vertical electron affinities (EA<sub>v</sub>).

								
	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>
EA <sub>v</sub> [eV]	7.18	6.73	7.33	6.64	7.19	6.75	6.59	6.03
	H Abs 100%	H Abs 100%	H Abs 100%	H Abs 100%	H Abs 100%	H Abs 100%	H Abs 100%	H abs 100%
	eff. = 89%	eff. = 50%	eff. = 77%	eff. = 45%	eff. = 67%	eff. = 43%	eff. = 46%	eff. = 20%
	SCH <sub>3</sub> Abs 100%	SCH <sub>3</sub> Abs 100%	SCH <sub>3</sub> Abs 100%	SCH <sub>3</sub> Abs 100%	SCH <sub>3</sub> Abs 100%	SCH <sub>3</sub> Abs 100%	SCH <sub>3</sub> Abs 95% e <sup>-</sup> abs 2% H abs 2% SSCH <sub>3</sub> abs 1%	SCH <sub>3</sub> Abs 98% H abs 2%
	eff. = 100%	eff. = 90%	eff. = 95%	eff. = 88%	eff. = 93%	eff. = 86%	eff. = 90%	eff. = 83%

[a] Reaction efficiency (eff.; % of collisions leading to reaction) =  $k_{\text{reaction}}/k_{\text{collision}} \times 100$ ; precision +/–10%; accuracy +/–50%. [b] abs = abstraction. [c] Experimental data for **11** and **12** taken from ref. 14. [d] Values calculated at the CASPT2/CASSCF(m,n)/cc-pVTZ//CASSCF(m,n)/cc-pVTZ level of theory.

increases the reactivity of all these radicals when compared to their unsubstituted counterparts by increasing their  $EA_v$  (Table 2).

All cyano-substituted *para*-benzyne analogs are substantially less reactive than the analogous monoradicals. This finding is in agreement with their singlet ground states hindering radical reactivity.<sup>[7,8]</sup> The reactivity observed for *para*-benzyne analogs **1–4** shows similarities but also differences when compared to the analogous monoradicals. For example, instead of a single H atom abstraction from cyclohexane, the biradicals abstract two H atoms from one cyclohexane molecule (Table 1). The first H atom abstraction can also be accompanied by electron transfer (Table 1),<sup>[18]</sup> resulting in a product that appears to arise from hydride abstraction. In addition to H atom abstraction and electron transfer, the first H atom abstraction can be followed by radical-radical recombination, yielding a stable adduct as the final product. Proposed mechanisms for these reactions are shown in Scheme 1.



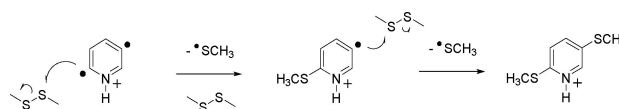
**Scheme 1.** Proposed mechanisms for two H atom abstractions,<sup>[14]</sup> H atom abstraction followed by electron transfer,<sup>[18]</sup> and H atom abstraction followed by radical-radical recombination for biradical **2** upon reactions with cyclohexane.

Observation of two H atom abstractions is consistent with *para*-benzynes containing two radical sites (i.e., they have not undergone retro-Bergman ring-opening). This reaction has been calculated (at the RHF-BCCD(T)/cc-pVTZ//UB3LYP/cc-pVTZ level of theory) to be highly exothermic for **1** ( $-84 \text{ kcal mol}^{-1}$ ).<sup>[14]</sup>

The lowest reactivity was observed for the unsubstituted analog **1**. This biradical has a S–T splitting that is similar to that of the cyano-substituted biradical **2** ( $-5.3$  vs.  $-4.8 \text{ kcal mol}^{-1}$ , respectively; Table 1). However, **2** reacts 20 times faster with cyclohexane than **1** (Table 1). This finding indicates that the critical rate-controlling parameter here is not the S–T splitting, as has been suggested.<sup>[7,8]</sup> On the other hand, the  $EA_v$  values of **1** and **2** are significantly different ( $6.65 \text{ eV}$  and  $7.25 \text{ eV}$ , respectively; Table 1). Thus, the greater  $EA_v$  likely explains the greater reactivity of **2**. Further support for this hypothesis is provided by the observation of essentially identical reaction efficiencies for **2–4** (1–2%; Table 1), all with a similar  $EA_v$ .

The cyano-substituted biradicals are also more reactive toward dimethyl disulfide than the unsubstituted biradical (Table 1), as expected based on above discussion. Two consecutive abstractions of a  $\text{SCH}_3$  group from two dimethyl disulfide

molecules were observed for all four biradicals (for likely mechanisms, see Scheme 2). The primary abstraction likely



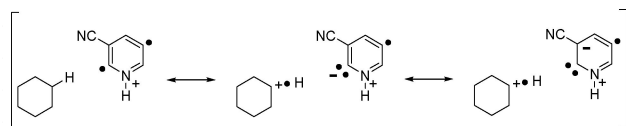
**Scheme 2.** Proposed mechanisms for two  $\text{SCH}_3$  abstractions by biradical **1** upon reaction with two dimethyl disulfide molecules.

occurs at the more reactive radical site (C-2; see discussion above), and the secondary reaction quenches the remaining radical site at C-5. This reaction sequence dominates or is among the two dominant reactions for **1**, **3** and **4** but not for **2** (Table 1). The reasons for this behavior are not clear at this time.

Large amounts of proton transfer products were observed for the three cyano-substituted biradicals when allowed to react with dimethyl disulfide. This reactivity reflects the low (calculated) proton affinities (PA) of their conjugate bases ( $< 188 \text{ kcal mol}^{-1}$ ; Table 1) relative to that of dimethyl disulfide<sup>[19]</sup> ( $PA = 194.9 \text{ kcal mol}^{-1}$ ). On the other hand, the unsubstituted biradical **1** shows no proton transfer, as expected, since this reaction would be endothermic ( $PA(\mathbf{1}) = 198.9 \text{ kcal mol}^{-1}$ ; Table 1). The same is true for the cyano-substituted monoradicals; for example, the (calculated) PA of the conjugate base of the 3-cyano-2-dehydropyridinium cation is  $197.1 \text{ kcal mol}^{-1}$  (same level of theory as described in Table 1). Endothermic bimolecular reactions do not generally occur under the conditions employed here. The experimental results demonstrate that exothermic proton transfer can dominate over fast radical reactions for protonated *para*-benzynes, which is not surprising because the proton transfer reactions are likely to be barrierless while the radical reactions are not.

Comparison of the reactivities of the unsubstituted (**1**) and cyano-substituted biradicals (**2–4**) toward dimethyl disulfide is complicated by the fact that most of the substituted species undergo predominant proton transfer and not radical reactions. However, biradical **4** shows equally fast  $\text{SCH}_3$  group abstraction and proton transfer. Therefore, one may consider approximately half of the reaction efficiency (41%) to correspond to the radical reaction. This is still about 26 times greater efficiency than that measured for **1**, again supporting the hypothesis that  $EA_v$  is the reactivity-controlling factor for these *para*-benzynes.

In conclusion, the reactivity of a *para*-benzyne analog (**1**) and its three cyano-substituted derivatives (**2–4**) toward cyclohexane and dimethyl disulfide was studied in a modified dual-linear quadrupole ion trap. The presence of two radical sites in all biradicals was confirmed through observation of two atom or group abstraction reactions. All cyano-substituted biradicals react substantially faster than the unsubstituted analog, which is rationalized by their greater (calculated)  $EA_v$  rather than by differences in their S–T splittings. The greater  $EA_v$  is likely to lead to a more stable transition state due to stabilization of a ditterionic resonance structure (charge transfer resonance structure; for example, see Scheme 3), just like for polar monoradicals.<sup>[17,22]</sup>



**Scheme 3.** Proposed dritterionic resonance structures for the transition state of the H atom abstraction reaction by biradical **3**.

Fast proton transfer to dimethyl disulfide was observed for the cyano-substituted biradicals, which demonstrates that exothermic proton transfer can compete with fast radical reactions for acidic *para*-benzyne cations. Finally, the reactivity of all the biradicals is substantially lower than that of the related monoradicals. This finding is consistent with the hypothesis that singlet ground states of biradicals hinder radical reactions.<sup>[7,8]</sup>

## Experimental Section

2,5-Diiodopyridine and all monoradical precursors were purchased from commercially available sources and used without further purification. The other biradical precursors were synthesized from commercially available compounds. Detailed synthesis procedures, <sup>1</sup>H and <sup>13</sup>C-NMR and MS data as well as X-ray structures are provided in the Supporting Information. All gas-phase reactions were carried out in a differentially pumped dual-LQIT tandem mass spectrometer<sup>[15]</sup> (DLQIT) equipped with a manifold for reagent introduction designed based on a previously described apparatus.<sup>[21]</sup> 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 precursors were introduced and ionized by protonation via atmospheric pressure chemical ionization (APCI) and the radical sites were formed by homolytic cleavage of carbon-iodine bonds induced through in-source collision-activated dissociation 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.<sup>[9]</sup> The product branching ratios are product distributions at short reaction times where secondary reactions do not yet take place. Secondary products were confirmed by re-isolating primary products and allowing them to undergo further reactions with the reagent of interest.

## Acknowledgements

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Biradical · electron affinities · gas-phase reactions · mass spectrometry · *para*-benzyne

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