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Substituent effects on benzyne electronic structures

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epoc ABSTRACT: The effect of inductive strength and π-conjugating tendency on the structure and energetics of singly substituted benzynes is studied for different substituents. For amino and cyano substituents, all possible isomers are examined. For silyl and ammonio substituents, *meta* isomers are examined. Copyright © 2001 John Wiley & Sons, Ltd.

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KEYWORDS: aryne; singlet–triplet splitting; resonance; biradical; diradical; modeling

INTRODUCTION

Arynes are useful as synthetic reagents[1,2] and they are also key intermediates responsible for the cytotoxicity of the enediyne class of antitumor antibiotics.[3–5] In particular, a *p*-benzyne reactive intermediate can be generated by Bergman cyclization[6,7] of the metastable enediyne functionality after binding to cellular DNA. This highly reactive diradical abstracts two hydrogen atoms from ribose moieties, one from each backbone of the DNA double helix. The resulting lesions result in irreparable double-stranded cleavage, and there is thus much interest in tuning the reactivity and selectivity of enediyne-based drugs so that they may be more selectively targeted. Insofar as such efforts typically involve substitution of the *p*-benzyne framework with one or more substituents, the fundamental effects of such substitution on the structure and reactivity of the diradical are of significant interest. From a physical organic standpoint, substitution effects on arynes in general are of interest to the extent they influence the properties of these reactive intermediates. In this work, we examine a series of singly substituted benzynes in an attempt to deduce what effects σ- and π-donors and -acceptors have on the lowest energy singlet and triplet states for all isomers of these molecules.

The three isomers of the parent benzyne molecule are well known and have been characterized thoroughly both experimentally[8–10] and by approximate solution of the Schrödinger equation.[11–18] Substituted arynes have been less completely characterized, although experimental[19–22] and computational[22–28] studies have been reported for several. The effect of heteroatomic substitution within the ring has also seen substantial study.[18,29–35] We recently reported a detailed computational study of the ten didehydrophenols, i.e. those benzynes derived from exocyclic substitution by a hydroxyl group.[28] In this work a more complete set of substituents is examined in order to span a wider region of chemical space with respect to the substituent properties. In particular, we computationally characterize all possible didehydroanilines (DDAs) and didehydrobenzonitriles (DDBNs). To illuminate particular details associated with singlet *meta* benzynes, we also characterized the singlet *meta* isomers of the didehydrophenylammonium cation (DDPA$^+$), and didehydrophenylsilane (DDPS).

COMPUTATIONAL METHODOLOGY

Geometries were optimized at the multiconfigurational self-consistent-field (MCSCF) and density functional theory (DFT) levels. In every case the correlation-consistent polarized valence-double-ζ basis set, cc-pVDZ,[36] was employed.

The MCSCF calculations were of the complete active space SCF (CASSCF) variety.[37] For the arynes, eight electrons were included in the active space constructed from the six π orbitals of the aromatic ring and the two σ radical orbitals. This active space was reduced to seven electrons/orbitals for the substituted phenyl radicals, and to six electrons/orbitals for substituted benzenes when analysis of such species proved appropriate.

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The DFT functional employed combined the gradient-corrected exchange functional of Becke[38] with the gradient-corrected correlation functional of Lee *et al.*[39] (BLYP). Singlet aryne DFT "wave functions" that exhibited instability with respect to spin-symmetry breaking were reoptimized with an unrestricted self-consistent-field formalism. Vibrational frequencies, zero-point vibrational energies, and thermal enthalpy contributions were calculated at the (U)BLYP/cc-pVDZ level.

Dynamic electron correlation was also accounted for at the CASPT2 level[40,41] using the MCSCF wave functions as the reference. Some caution must be applied in interpreting the CASPT2 results, since this level of theory is known to suffer from a systematic error proportional to the number of unpaired electrons.[42] CASPT2 energies were calculated for both MCSCF and DFT geometries. In addition, coupled-cluster calculations[43,44] including single and double excitations and a perturbative estimate for triple excitations were carried out for single-configuration reference wave functions expressed in Brueckner orbitals (BD(T)[45]). Brueckner orbitals[46] eliminate contributions from single excitations in the coupled-cluster ansatz, and this can remove instabilities[47] associated with very large singles amplitudes in the more common CCSD(T) method. Such instabilities were manifest in many of the substituted phenyl radicals and arynes. We note that this is purely a mathematical technique to stabilize the solution of the truncated coupled-cluster equations, and in no way affects analysis of the reference wave functions.

Analysis of the CASPT2 and BD(T) energies for the MCSCF and BLYP geometries indicated that, in the overwhelming number of instances, the BLYP geometries were lower in energy (i.e. better, since they are closer to the minima on the corresponding correlated potential energy surfaces). Thus, unless otherwise indicated, all data in this paper are computed using the BLYP geometries. Geometries of the monoradicals were also optimized using the gradient-corrected correlation functional of Perdew et al.[48] (BPW91) for the sole purpose of calculating ^{1}H isotropic hyperfine splittings (*hfs*). Using previously published correlations between the BPW91/cc-pVDZ *hfs* and CASPT2/cc-pVDZ//CASSCF/cc-pVDZ singlet–triplet (S–T) splittings afforded cheap and accurate estimates for the latter quantities (*vide infra*). [The particular correlating equation is (S–T splitting, kcal mol^{-1}) = $a(^1\text{H hfs, G}) - b$, where for *ortho* and *meta* diradicals $a = -1.39$ and $b = -9.48$ and for *para* diradicals $a = -1.99$ and $b = -0.30$.] We note that Sander and Exner have also compared various functionals for their accuracy in predicting substituted *m*-benzyne geometries and concluded that the BLYP functional was optimal.[22] Gräfenstein *et al.* have also shown that this level of theory compares well with experiment for unsubstituted arynes, noting that this agreement derives in part from a fortuitous cancellation of errors associated with basis set incompleteness and deficiencies in the functional.[49]

Isotropic hyperfine coupling constants (*hfs*) were calculated as[50]

$$a_X = (4\pi/3)\langle S_z\rangle^{-1} g g_X \beta \beta_X \rho(X) \qquad (1)$$

where g is the electronic g factor, β is the Bohr magneton, g_X and β_X are the corresponding values for nucleus X, and ρ(X) is the Fermi contact integral

$$\rho(\mathrm{X}) = \sum_{\mu\nu} P_{\mu\nu}^{\alpha-\beta} \phi_\mu(\boldsymbol{R}_\mathrm{X}) \phi_\nu(\boldsymbol{R}_\mathrm{X}) \qquad (2)$$

where $\mathbf{P}^{\alpha-\beta}$ is the BPW91/cc-pVDZ one-electron spin-density matrix, and evaluation of the overlap between basis functions ϕ_μ and ϕ_ν is only at the nuclear position $\boldsymbol{R}_\mathrm{X}$.

Multi- and single-reference calculations were carried out with the MOLCAS[51] and Gaussian 98[52] electronic structure program suites respectively.

NOMENCLATURE

We adopt a naming convention where the substituted carbon atom is assigned to be position 1, and numbering proceeds around the ring so as to provide the lowest possible number to the dehydrocenter nearest the point of substitution. Thus, the analogs of *o*-benzyne are 2,3- and 3,4-didehydro species, the analogs of *m*-benzyne are 2,4-, 2,6-, and 3,5-didehydro species, and the analogs of *p*-benzyne are 2,5-didehydro species. As the substituents studied here are all symmetric with respect to a plane perpendicular to and bisecting the aromatic ring, there are no issues associated with substituent rotational isomerism.

RESULTS

The various theoretical energies were processed in a series of isodesmic reactions in order to achieve chemically interpretable accuracy. First, biradical stabilization energies (BSEs) for the singlet and triplet benzynes were computed. The BSE is the 298 K enthalpy change for

$$m\text{-C}_6\text{H}_4\text{R} + n\text{-C}_6\text{H}_4\text{R} \rightarrow m,n\text{-C}_6\text{H}_3\text{R} + \text{C}_6\text{H}_5\text{R} \qquad (3)$$

where m and n represent the dehydro positions. Thus, Eqn. (3) measures the difference in enthalpy associated with having both radicals in the same molecule compared with having the radicals individually located at the identical positions in corresponding monoradicals. We then correct the raw BSE values by the amount required to bring the analogous isodesmic equation for the corresponding

Table 1. Singlet benzyne BSEs[a]

		BSE (H_{298}, kcal mol^{-1})					
		ortho		*meta*			*para*
Benzyne	Theory	2,3	3,4	2,6	3,5	2,4	2,5[b]
DDA (R=NH_2)	BLYP	−38.0	−34.4	−25.8	−23.5	−18.1	−3.4
	CASPT2	−37.2	−34.6	−24.8	−22.1	−18.5	−3.1
	BD(T)	−35.3	−34.6	−25.1	−22.7	−18.5	−3.2
DDBN (R=CN)	BLYP	−36.3	−35.3	−20.8	−20.7	−20.6	−3.8
	CASPT2	−35.9	−35.4	−20.7	−20.4	−19.6	−3.6
	BD(T)	−34.4	−33.9	−19.0	−19.0	−18.7	−2.6
DDPS (R=SiH_3)	BLYP			−20.6	−20.1	−20.9	
	CASPT2			−20.1	−20.0	−21.3	
	BD(T)			−20.6	−20.1	−21.2	
DDPA (R = NH_3^+)	BLYP			−23.5	−21.7	−23.4	
	CASPT2			−23.2	−20.3	−21.1	
	BD(T)			−23.0	−20.8	−22.5	

[a] At optimized BLYP/cc-pVDZ geometries; see Eqn. (3) for definition of BSE.
[b] Geometry optimized with unrestricted (broken-spin-symmetry) BLYP.

benzyne (i.e. R = H) into agreement with experiment for the particular level of theory.[9] [The experimental BSEs (H_{298}, kcal mol^{-1}) for *o*-, *m*-, and *p*-benzyne are -35.6 ± 3.6, -20.6 ± 3.6, and -4.2 ± 2.1 respectively for the singlet state, and 2.1 ± 3.6, 0.8 ± 2.8, and -0.4 ± 2.2 respectively for the triplet state. The experimental S–T splittings (H_0, kcal mol^{-1}) are -37.5 ± 0.3, -21.0 ± 0.3, and -3.8 ± 0.5 respectively. The experimental heats of formation (H_{298}, kcal mol^{-1}) of benzene and the phenyl radical are 19.7 ± 0.2,[53a] and 81.2 ± 0.6[53b] respectively.] This method largely removes any idiosyncratic behavior associated with the various levels of theory in this paper; indeed, the span of the predicted BSEs, listed in Tables 1 and 2 for the singlets and triplets respectively, is typically on the order of 1 kcal mol^{-1} or less. Naturally, this scheme is reliant upon the substitution on the aromatic ring being regarded as a small perturbation on the parent benzyne, and may be expected to break down in situations that fail to conform to this relationship.

The differences in BSEs for the singlet and triplet spin states define the 298 K S–T splittings. Experimentally, such splittings are more typically reported as 0 K quantities, and we follow that convention in Table 3 where S–T splittings for the DDAs and DDBNs are reported (the differential thermal contributions to the singlet and triplet spin states at 298 K are rarely more than 0.1 or 0.2 kcal mol^{-1} in any case). Applying the BSE correction scheme outlined above is equivalent to calculating the reaction enthalpy difference between the singlet and triplet states for

$$m,n\text{-}C_6H_4 + C_6H_5R \rightarrow m,n\text{-}C_6H_3R + C_6H_6 \qquad (4)$$

and then adding this quantity to the experimental value[9,53] for the S–T splitting of the appropriate unsubstituted benzyne. Again, the efficacy of this procedure is evident in the narrow range of splittings predicted by the various levels of theory in Table 3.

An estimation of the S–T splitting based on the use of antecedent radical ^{1}H hyperfine coupling constants is also presented in Table 3. In aryl radicals, the magnitude of the *hfs* predicted for a particular H atom has been found to

Table 2. Triplet benzyne BSEs[a]

		BSE (H_{298}, kcal mol^{-1})					
		ortho		*meta*			*para*
Benzyne	Theory	2,3	3,4	2,6	3,5	2,4	2,5
DDA (R=NH_2)	BLYP	2.1	1.5	0.4	1.0	−0.1	−1.0
	CASPT2	5.4	2.5	3.2	1.2	0.0	−0.8
	BD(T)	4.9	2.6	2.9	1.2	0.0	−0.9
DDBN (R=CN)	BLYP	2.1	2.0	1.3	1.1	0.6	−0.7
	CASPT2	1.8	2.1	1.2	0.9	0.6	−0.6
	BD(T)	3.3	3.6	2.7	2.4	2.2	0.9

[a] At optimized BLYP/cc-pVDZ geometries; see Eqn. (3) for definition of BSE.

Table 3. Benzyne S–T splittings[a]

		S–T (H_0, kcal mol^{-1})					
		ortho		*meta*			*para*
Benzyne	Theory	2,3	3,4	2,6	3,5	2,4	2,5[b]
DDA (R=NH_2)	BLYP	−38.2	−35.7	−26.5	−24.6	−18.1	−2.5
	CASPT2	−42.5	−36.9	−28.2	−23.5	−18.7	−2.3
	BD(T)	−40.1	−37.0	−28.3	−24.0	−18.7	−2.4
	hfs corr.[c]	−40.4	−36.6	−25.3	−22.2	−19.1	−2.9
DDBN (R=CN)	BLYP	−39.0	−37.3	−21.8	−21.4	−20.9	−3.1
	CASPT2	−38.3	−37.5	−21.6	−21.0	−20.0	−3.0
	BD(T)	−38.3	−37.5	−21.3	−21.2	−20.6	−3.4
	hfs corr.[c]	−39.1	−37.7	−22.0	−20.7	−20.1	−3.8

[a] At optimized BLYP/cc-pVDZ geometries unless otherwise indicated; see also Eqn. (4) and accompanying text.

[b] Singlet geometry optimized with unrestricted (broken-spin-symmetry) BLYP.

[c] At optimized BPW91/cc-pVDZ geometries; see Computational Methodology.

correlate with the magnitude of the S–T splitting for the diradical that would be generated by abstraction of that H atom. Thus, for instance, the *hfs* for the proton at position 3 in the 2-dehydroaniline radical can be used to predict the S–T splitting in 2,3-DDA (and so too that at position 2 in the 3-didehydroaniline radical; as per the correlating equations noted above).[16,18,27,28] The S–T splittings generated in this way were then corrected by the same amount needed to bring the estimated S–T splitting for the corresponding benzyne into agreement with experiment. The overall agreement between direct computation and this estimation technique is exceptional. The ease with which one may generate the small amount of data needed to estimate the S–T splittings using the *hfs*

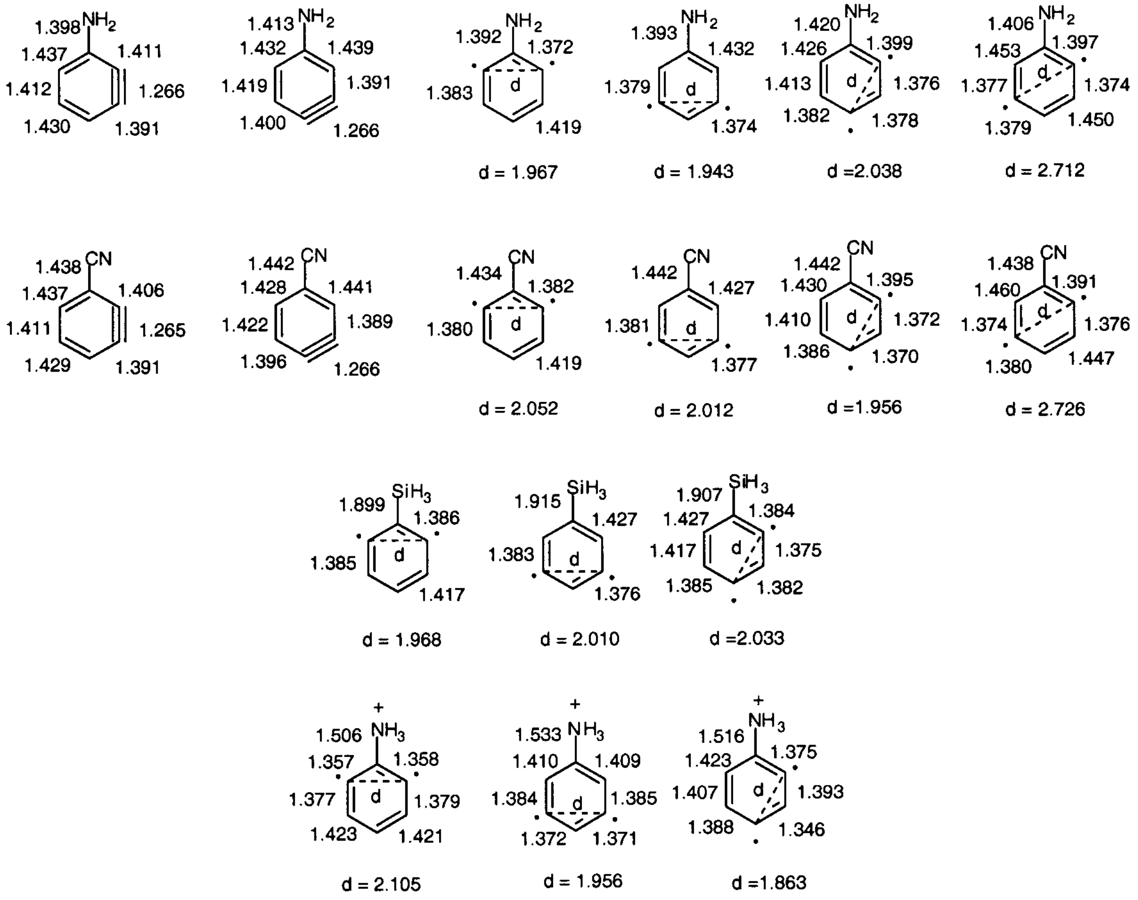


Figure 1. Optimized geometries (BLYP/cc-pVDZ) of singlet benzynes. The substituents are identified as group R in the tables

correlation makes this methodology particularly appropriate for larger systems and for rapid surveys of smaller systems.

In order to ascertain the origin of various changes in BSEs as a function of substitution, it is helpful to consider changes in molecular geometries as well. Unique heavy atom bond distances for all singlet arynes are presented in Fig. 1. The geometries of the triplet DDAs and DDBNs are not particularly perturbed relative to their unsubstituted analogs, so they are not presented or discussed; they are, however, provided as supporting information.

DISCUSSION

To facilitate discussion, we will hereafter refer only to CASPT2 energies. This level of theory provides results that are closest to the average over the reasonably narrow span of all of the theoretical predictions. Note, however, that the good agreement between different levels of theory relies on having used an isodesmic correction scheme—in the absence of such an approach there is no reason to expect CASPT2 to be better than DFT or BD(T). We begin with a discussion of some geometric effects common to all of the diradicals, then focus on particular substitution effects influencing the individual *ortho, meta,* and *para* benzynes.

Common geometric effects

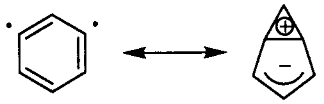
In every isomer, regardless of spin state, C—C bonds to the radical centers shorten and bonds antiperiplanar to these centers lengthen. The radical centers preferentially increase the s character in their C—C bonds at the expense of their singly occupied orbital, and this leads to bond shortening. Furthermore, the radical centers hyperconjugate with the σ and σ^* orbitals of the antiperiplanar C—C bonds, with the singly occupied orbital acting as a donor *into* the σ^*_{CC} and an acceptor *from* the σ_{CC}.[11,54] As both interactions decrease the bond order of the antiperiplanar bond, it lengthens. As the hyperconjugative overlap between the radical orbital and the ring σ orbitals is net bonding, this is a second factor that shortens C—C bonds to the radical centers. In *ortho* and *meta* benzynes, the particular locations of the radicals can cause these various effects to oppose one another and possibly cancel, but in the *para* benzynes they reinforce one another, and those rings are thus significantly distorted. The longest C—C bond lengths are those that are antiperiplanar to both radical centers in 2,5-DDA and 2,5-DDBN, 1.453 Å and 1.460 Å respectively.

The *ortho* diradicals

The 3,4-benzynes are essentially unaffected by substitution. The singlet and triplet BSEs for 3,4-DDA and 3,4-DDBN are all within 1 kcal mol^{-1} of the experimental values[9,53] for unsubstituted *o*-benzyne. The same insensitivity has already been noted in 3,4-didehydrophenol.[28] The 2,3-benzynes, on the other hand, do show singlet BSE variations as a function of the aryl substituent. The bent in-plane π bond of the aryne is highly polarizable and can stabilize partial positive charge at position C1 by increasing electron probability density on the adjacent carbon C2 (presumably it could also polarize in the opposite direction to stabilize partial negative charge at position C1, but we do not study any *ortho* isomers substituted with strong σ donors here). This polarization leads to significant distortions in the geometry of the ring. The radical orbital at C2 increases in s character in order to stabilize the increased amount of charge (i.e. it becomes more carbanion-like), which results in a more acute C1—C2—C3 bond angle. The reverse is true at C3: the relative dearth of electron density results in a more obtuse bond angle as s character is invested in this position's bonding orbitals in preference to its depleted "non-bonding" orbital. The difference between the C2 and C3 bond angles is 17° for R = OH,[28] 11° for R = NH$_2$, and only 5° for R = CN. This trend qualitatively tracks the σ-withdrawing power of the three substituents. The same trend is reflected in the difference in S–T splittings for the 2,3-versus the 3,4-isomers. The former enjoy an increasingly larger stabilization of the singlet with stronger σ electron-withdrawing groups, whereas the latter are effectively insulated from substitution effects. As the stabilizing polarization is not available to the triplet (at least not within the frontier orbitals, since the non-bonding electrons have the same spin), the S–T splittings of the 2,3-isomers are larger than that of *o*-benzyne, whereas the unmodulated S–T splittings of the 3,4-isomers are essentially identical to that of *o*-benzyne.[9,28,53]

The *meta* diradicals

The geometries and energies of the various substituted *meta* isomers can best be understood by considering the resonance between diradical and zwitterionic forms that is available to the singlets



(5)

(Note that the alternative zwitterionic mesomer having reversed charge is disfavored by the antiaromaticity of the cyclopropenyl anion and/or cyclopentadienyl cation combination.) Electron donors and acceptors cause the charge-separated resonance structure to contribute to the hybrid to a greater or lesser extent, depending on the location of substitution. Donors, such as OH, NH_2, and SiH_3, substituted on the three-membered ring (i.e. generating the 2,6-benzyne) stabilize the cyclopropenium cation. Thus, we see the 2,6-interdehydrocarbon distance is smallest with NH_2 and SiH_3 as substituents and longest with CN and NH_3^+ as substituents (Fig. 1), reflecting the greater contribution of the formally bicyclic mesomer to describing the benzynes substituted with electron-donating groups instead of electron-withdrawing groups.

By contrast, substituents on the termini of the allyl anion moiety in Eqn. (5) (i.e. 2,4-benzynes) interact not with a partial positive charge but with a negative one. Thus, acceptors such as NH_3^+ and CN better stabilize the zwitterionic mesomer and show the shortest 2,4-interdehydrocarbon distances, whereas donors like NH_2 and SiH_3 are destabilizing, and show the longest such distances (Fig. 1).

Finally, in the case of the 3,5-benzynes, the allyl anion is negatively charged but the central carbon is polarized to be slightly positive by the build-up of anionic density primarily at the termini. Thus, it is expected that the zwitterionic mesomer will be best stabilized by σ-electron-withdrawing groups and π-electron-donating groups. Conforming to this analysis, the 3,5-interdehydrocarbon distance is shortest for the corresponding DDA isomer, next shortest for the DDPA isomer, and longest for the more weakly perturbed DDBN and DDPS isomers.

Trends in isomer energetics largely follow the lines expected based on the above analysis. Thus, for instance, the largest singlet BSE for a 2,6-benzyne is that predicted for DDA, the largest singlet BSE for a 2,4-benzyne is that predicted for DDPA, and the largest singlet BSE for a 3,5-benzyne is that predicted for DDA. Another factor influencing energetics appears to be electrostatic in nature. Over all benzyne isomers, population analysis indicates that there is a tendency for the radical positions each to be about 0.1 units more negatively charged than the remaining CH fragments of the aromatic ring. This seems to be the factor making 2,6-DDPA somewhat more stable than 2,4-DDPA, even though the resonance analysis above would suggest the opposite ordering.

Note that, owing to the enormous flexibility of *meta* arynes,[15,21,22,25,28,33] the different geometric trends discussed above are not necessarily associated with very large energetic consequences. Recalling that the singlet BSE for *m*-benzyne is $-20.6\ \mathrm{kcal\ mol^{-1}}$,[9,53] Table 1 indicates that eight of the 12 substituted benzyne isomers discussed here have singlet BSEs predicted to be within $1\ \mathrm{kcal\ mol^{-1}}$ of that value, and must therefore be considered to be energetically unaffected by substitution to within the combined theoretical and experimental errors.

The *para* diradicals

The predicted S–T splittings for 2,5-DDA and 2,5-DDBN are smaller than that found for *p*-benzyne.[9,53] The difference is largest for the DDA, rather small for DDBN, and has been predicted to be of intermediate magnitude for 2,5-didehydrophenol.[28] We rationalize this effect as deriving from selective triplet stabilization in these isomers by strongly inductive substituents. In particular, the empty C_{ipso}—X σ^* orbital (where X represents the substituent) mixes slightly with the molecular orbital (MO) derived from symmetric combination of the two nonbonding orbitals. The latter MO is the higher energy linear combination of the nonbonding orbitals, and is formally empty in the singlet state and singly occupied in the triplet.[11,15] Thus, the interaction favors the triplet and reduces the S–T splitting.

CONCLUSIONS

Substituent effects in the benzynes manifest themselves both inductively and conjugatively. Usually, the singlet states are the most sensitive to substitution and are selectively stabilized over the triplets to the greatest extent according to the following rules:

- the 2,3-isomer is better stabilized by σ-withdrawing/π-withdrawing groups;
- the 2,4-isomer is better stabilized by σ-withdrawing/π-withdrawing groups;
- the 2,6-isomer is better stabilized by σ-withdrawing/π-donating groups;
- the 3,5-isomer is better stabilized, albeit only weakly, by σ-withdrawing/π-donating groups.

When substitution is exactly contrary to the above rules, the singlet is *de*stabilized relative to the triplet. When the above rules are followed only partially, intermediate effects in either direction may be noted. The 3,4-isomers are, for the most part, insensitive to substitution.

In the 2,5-isomer, substitution effects tend to be small. However, the presence of a strong σ-withdrawing substituent can selectively stabilize the triplet over the singlet by hyperconjugative interaction.

SUPPORTING INFORMATION AVAILABLE

Electronic energies and structures for all species from all levels of theory are available electronically on the EPOC website.

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