Reactivity of Aromatic σ,σ -Biradicals Toward Riboses

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The gas-phase reactions of sugars with aromatic, carbon-centered σ,σ -biradicals with varying polarities [as reflected by their calculated electron affinities (EA)] and extent of spin-spin coupling [as reflected by their calculated singlet-triplet (S-T) gaps] have been studied. The biradicals are positively charged, which allows them to be manipulated and their reactions to be studied in a Fourier-transform ion cyclotron resonance mass spectrometer. Hydrogen atom abstraction from sugars was found to be the dominant reaction for the biradicals with large EA values, while the biradicals with large S-T gaps tend to form addition/elimination products instead. Hence, not all σ,σ -biradicals may be able to damage DNA by hydrogen atom abstraction. The overall reaction efficiencies of the biradicals towards a given substrate were found to be directly related to the magnitude of their EA values, and inversely related to their S-T gaps. The EA of a biradical appears to be a very important rate-controlling factor, and it may even counterbalance the reduced radical reactivity characteristic of singlet biradicals that have large S-T gaps. (J Am Soc Mass Spectrom 2006, 17, 1325–1334) © 2006 American Society for Mass Spectrometry

Aromatic carbon-centered σ -radicals (e.g., phenyl radicals) and σ,σ -biradicals (e.g., benzynes) have attracted a great deal of recent interest because of their role in nonhydrolytic DNA damage [1]. For example, some σ,σ -biradicals have been identified as the biologically active intermediates of the enediyne class of antitumor antibiotics [2]. These intermediates are believed to irreversibly damage double-stranded DNA via hydrogen atom abstraction from a sugar moiety in each strand [2]. Therefore, a better understanding of the factors controlling the reactivity of these biradicals toward sugars is important.

Solution [3] and gas-phase [4] studies on the reactivity of neutral and charged phenyl radicals have confirmed that these monoradicals can abstract hydrogen atoms from sugars as well as from the sugar moiety in nucleosides and dinucleoside phosphates. Polar effects (i.e., polarization of the transition state) play a major role in controlling these reactions [5–7]. However, no such studies have been reported for the analogous biradicals.

The magnitude of the singlet-triplet (S-T) gap has

been proposed earlier [8] as the major reaction rate controlling factor for aromatic σ,σ -biradicals with singlet ground states. As the magnitude of the S-T gap increases, the reaction efficiency for hydrogen atom abstraction from simple substrates has been observed to decrease, presumably because of the energetically high cost of uncoupling the biradical's electrons in the transition state [8, 9]. Biradicals with large S-T gaps appear to avoid this penalty by undergoing nucleophilic or electrophilic (nonradical) addition reactions [10]. Recent gas-phase studies have shown that in addition to S-T gap effects [9], reactions of biradicals with simple organic substrates are also sensitive to polar effects (which is reflected by the biradical's calculated vertical electron affinity, EA) [11]. Here, we report an examination of the reactivity of several σ,σ -biradicals (Scheme 1) toward various sugars, and show that these reactions are also affected by the S-T gap and the EA of the biradical.

Experimental

All experiments were carried out in a Finnigan model FTMS 2001, 3-tesla dual-cell Fourier-transform ion cyclotron resonance mass spectrometer (FT-ICR). The instrument has been described in detail previously [12].

The (bi)radical precursors, 4,6-dinitroisoquinoline, 5,8-dinitroisoquinoline, 5,7-dinitroquinoline, and 4-iodoisoquinoline, were synthesized using known methods [13]. They were introduced into the dual cell via a

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Scheme 1

heated solid probe at a nominal pressure of about $1.0\text{--}2.0 \times 10^{-8}$ torr.

Generation of (bi)radicals **1a–4a** (Scheme 1) involved *N*-protonation of the precursors, 4,6-dinitroisoquinoline, 5,8-dinitroisoquinoline, 5,7-dinitroquinoline, or 4-iodoisoquinoline, respectively, via methanol chemical ionization, whereas the generation of **1b–4b** involved *N*-methylation of the same precursors via methyl iodide chemical ionization. The *N*-protonated and *N*-methylated precursors, generated in one side of the dual cell, were transferred into the other cell by grounding the conductance limit plate for about 154 μs . The transferred ions were allowed to cool for 1 s via IR emission and collisions with the neutral sugar molecules (e.g., D-ribose at about 2.7×10^{-8} torr). The technique of sustained off-resonance irradiated collision-activated dissociation [14] (SORI-CAD) was used to homolytically cleave the carbon–iodine and/or carbon–nitrogen bonds to generate the corresponding (bi)radicals. This was accomplished by introducing argon (at a nominal pressure of about 10^{-6} torr) into the cell via a pulsed valve assembly. The ions were accelerated by continuously exciting them for one second at a frequency 1 kHz higher than their cyclotron frequency, and activated via collisions with argon. The (bi)radicals were then isolated by applying a series of stored-waveform inverse Fourier-transform [15] (SWIFT) excitation pulses to the plates of the cell to eject unwanted ions from the cell.

The isolated (bi)radical ions of interest were allowed to react with D-ribose, 2-deoxy-D-ribose, and 1-O-methyl-2-deoxy-D-ribose (at a nominal pressure of 1.0×10^{-8} to 1.2×10^{-7} torr) for variable periods of time (typically 1 to 900 seconds). Ion excitation for detection was achieved using a “chirp” of bandwidth 2.56 MHz and a sweep rate of 3200 Hz/ μs . Each spectrum was collected as 64 k data points with one zero fill before Fourier transformation. All measured reaction spectra were background-corrected as reported earlier [5]. A background reaction spectrum was collected in the absence of the isolated ion of interest. This spectrum was then subtracted from the reaction spectrum to remove peaks that are not indicative of the isolated ion’s reaction products. The product branching ratios were derived from the constant abundance ratios of the product ions at short reaction times.

The sugars, D-ribose, 2-deoxy-D-ribose, and 1-O-methyl-2-deoxy-D-ribose, were introduced into the instrument via a solids probe. The nominal pressure for each sugar was measured by an ion gauge and the pressure reading was corrected for the sensitivity [16] of the ion gauge towards each sugar and the pressure gradient between the cell and the ion gauge. The correction factor for each sugar was obtained by measuring the rate of the highly exothermic electron-transfer to ionized carbon disulfide (i.e., every collision is assumed to lead to a reaction). The concentration of the sugars is much greater than that of the radical ions in the cell. Hence, the reactions studied here follow pseudo-first-order kinetics. A semilogarithmic plot of the relative abundance of the reactant ion as a function of time, and knowledge of the concentration of the neutral reagent, yield the second-order reaction rate constants. The reaction efficiency is given as $k_{\text{reaction}}/k_{\text{collision}} \cdot k_{\text{collision}}$ was obtained via a parameterized trajectory theory [17]. The accuracy of the reaction efficiencies is estimated to be $\pm 50\%$ whereas the precision is estimated to be $\pm 10\%$.

Computational Methods

Molecular geometries and S-T gaps for the (bi)radicals were obtained as previously described [18]. To compute vertical EAs for the (bi)radicals, single-point DFT calculations were carried out for the ground states of these species using the augmented, correlation-consistent polarized valence-double- ζ (aug-cc-pVDZ [19] basis set (i.e., UBLYP/aug-cc-pVDZ). In almost all cases, these calculations were carried out for the UBLYP/cc-pVDZ optimized geometries. However, for the *meta*-biradicals, **3a** and **3b**, it was necessary to use the MCSCF/cc-pVDZ geometries because the UBLYP/cc-pVDZ structures were bicyclic. In general, then, these electronic energies are of either the UBLYP/aug-cc-pVDZ//UBLYP/cc-pVDZ or UBLYP/aug-cc-pVDZ//MCSCF/cc-pVDZ variety. Similar calculations were 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

Scheme 2

orbitals) of each molecule [Note that, for these calculations, we are computing the electron affinity of the radical site and *not* the electron affinity of the *molecule*]. 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 ground states) [Because the monoradicals and biradicals studied here contain a formal positive charge on the nitrogen atom, the states that are produced when an electron is added to the nonbonding orbital of either a monoradical or a biradical are formally zwitterionic,

i.e., they contain localized positive (π) and negative (σ) charges]. For the monoradicals, the vertical EAs are given by $[E_0(\text{monoradical; doublet state})] - [E_0(\text{monoradical} + \text{electron; singlet state})]$, while for the biradicals the vertical EAs are given by $[E_0(\text{biradical; singlet state})] - [E_0(\text{biradical} + \text{electron; doublet state})]$. Note that because these are vertical electron affinities, zero-point vibrational energies (ZPVEs) and 298-K thermal contributions to the enthalpy are necessarily not included. All MCSCF and DFT calculations were carried out with the MOLCAS [20] and Gaussian 98 [21] electronic structure program suites, respectively.

Table 1. Calculated electron affinities (eV) and singlet-triplet gaps (kcal/mol) for 1a–3a and 1b–3b

	1a	2a	3a	1b	2b	3b
EA	5.99 ^a	5.73 ^a	5.26 ^b	5.82 ^a	5.59 ^a	5.03 ^b
S-T gap ^c	−0.8	−5.0	−17.5	−0.8	−5.0	−18.8

^aCalculated at the UBLYP/aug-cc-pVDZ//UBLYP/cc-pVDZ level of theory.

^bCalculated at the UBLYP/aug-cc-pVDZ//MCSCF(12,12)/cc-pVDZ level of theory.

^cRef. [18]: calculated at the CASPT2/cc-pVDZ//MCSCF(12,12)/cc-pVDZ level of theory.

Table 2. Reaction efficiencies^a and products^b of the reactions of (bi)radicals **1a–4a** with sugars

	D-ribose	2-deoxy-D-ribose	1-O-methyl-2-deoxy-D-ribose
1a	H abst. (2°) 2H abst.	H abst. (2°) 2H abst.	H abst. (2°) 2H abst.
	100%	100%	100%
	Eff.	Eff.	Eff.
	42% ^c	46% ^c	56% ^e
2a	Adduct	Adduct	Adduct 2H abst.
	100%	100%	83%
	Eff.	Eff.	Eff.
	1.3% ^f	0.70% ^g	0.45% ^c
3a	Adduct	Adduct	Adduct
	100%	100%	100%
	Eff.	Eff.	Eff.
	1.0%	0.43% ^c	Very slow
4a	H abst.	H abst.	H abst.
	100%	100%	100%
	Eff.	Eff.	Eff.
	32%	38%	34%

^aReaction efficiency (Eff.) = $k_{\text{reaction}}/k_{\text{collision}} \times 100\%$.^bProduct branching ratios are given after each primary reaction product.^cFrom nonlinear curve fit: ~20% of the reactant ion population was unreactive.^dUnidentified products.^eFrom nonlinear curve fit: ~5% of the reactant ion population was unreactive.^fFrom nonlinear curve fit: ~10% of the reactant ion population was unreactive.^gFrom nonlinear curve fit: ~40% of the reactant ion population was unreactive.

Results and Discussion

Reactivity Studies

Gas-phase reactions of the biradicals **1a–3a** and **1b–3b** and monoradicals **4a** and **4b** (Scheme 1) with D-ribose, 2-deoxy-D-ribose, and 1-O-methyl-2-deoxy-D-ribose were examined in an FT-ICR. The (bi)radicals were synthesized as shown in Scheme 2. The calculated S-T gaps and EAs for the biradicals are given in Table 1. Previously published studies [9, 11] have demonstrated that the biradicals **1** and **2** react exclusively via radical pathways, while radical **3** undergoes electrophilic addition/elimination reactions. The results for the reactions of the (bi)radicals with the various sugars are summarized in Tables 2 and 3. Note that earlier structural

characterization of gas-phase monosaccharides has revealed [22] that 1-O-methyl-2-deoxy-D-ribose has a five-membered ring structure, while D-ribose and 2-deoxy-D-ribose have six-membered ring structures.

The *N*-protonated biradical **1a** reacts almost exclusively via hydrogen atom abstraction with all of the sugars examined. The analogous *N*-methylated biradical **1b** reacts more slowly than **1a**, and yields significant amounts of addition/elimination products in addition to the hydrogen atom abstraction product. The reactions of **1b** with D-ribose and 2-deoxy-D-ribose appear to involve addition followed by one or two water losses, whereas reactions with 1-O-methyl-2-deoxy-D-ribose involve addition followed by loss of methanol, and loss of both methanol and

Table 3. Reaction efficiencies^a and products^b of the reactions of (bi)radicals **1b–4b** with sugars

	D-ribose	2-deoxy-D-ribose	1-O-methyl-2-deoxy-D-ribose
1b	H abst. 45% Adduct-H ₂ O 33% Adduct-2H ₂ O 22% Trace amount of H ₂ O abstraction	H abst. 35% Adduct-H ₂ O 11% Adduct-2H ₂ O 21% H ₂ O abst. 33%	H abst. 39% Adduct-CH ₃ OH 22% Adduct-CH ₃ OH-H ₂ O 31% H ₂ O abst. 8%
	Eff. 25% ^c	Eff. 32% ^c	Eff. 39% ^c
2b	No Reaction	No Reaction	No Reaction
3b	No Reaction	No Reaction	No Reaction
4b	H abst. 100% Eff. 23% ^d	H abst. 100% Eff. 17% ^d	H abst. 100% Eff. 13% ^d

^aReaction efficiency (Eff.) = $k_{\text{reaction}}/k_{\text{collision}} \times 100\%$.^bProduct branching ratios are given after each primary reaction product.^cFrom non-linear curve fit: ~20% of the reactant ion population was unreactive.^dFrom non-linear curve fit: ~40% of the reactant ion population was unreactive.

water. The reactions are likely initiated by hydrogen atom abstraction from the sugar molecule. Based on a recent publication [23], the bond between hydrogen and C-5 is the one with the lowest homolytic dissociation energy in 2-deoxyribofuranoses like 1-O-methyl-2-deoxy-D-ribose. However, breaking the bond of C-4 or C-3 to hydrogen is less than 2 kcal/mol more endothermic. Hence, any of these three bonds are possible candidates for the initial hydrogen atom abstraction step. If the hydrogen atom is abstracted from C-4, a reasonable mechanism can be presented for the consecutive losses of two water molecules (Scheme 3). After hydrogen atom abstraction, a fast radical–radical combination takes place. The excess energy gained by the system from this highly exothermic reaction results in a C–C bond cleavage followed by a 1,2-hydride shift which generates a more stable carbocation. Proton transfer from C-3 to the hydroxyl group bound to C-1 facilitates the loss of a water molecule. The proposal that the hydroxyl group bound to C-1 is the leaving group is supported by the fact that methanol loss, instead of

water loss, was observed for 1-O-methyl-2-deoxy-D-ribose. Further, 2-deoxy-D-ribose undergoes the loss of two water molecules just like D-ribose, which indicates that the C-2 hydroxyl group is not lost in these reactions. Hence, the second water loss likely occurs at the C-3 site.

The *N*-protonated biradical **2a** reacts very slowly with D-ribose via formation of a stable adduct (possibly via the same mechanism as **1a**, Scheme 3), while both adduct formation and hydrogen atom abstraction occur with 2-deoxy-D-ribose and 1-O-methyl-2-deoxy-D-ribose. The analogous *N*-methylated biradical **2b** does not react with any of the sugars. The same is true for the *N*-methylated biradical **3b**. The *N*-protonated biradical **3a** reacts extremely slowly with all the sugars via formation of a stable adduct. A previous study of the reactivity of biradical **3a** towards simple organic substrates demonstrated that **3a** reacts via nonradical pathways [9]. Therefore, formation of the adduct with each sugar is thought to occur via a nonradical electrophilic attack on the sugar (possibly as shown in Scheme 4). Mass spectra measured for the reactions of **1a**, **2a**, and

Scheme 3

3a, as well as the monoradical **4a**, with D-ribose are shown in Figures 1, 2, 3, and 4, respectively.

The trend for the overall reaction efficiency (Tables 2 and 3) observed for **1a** and **1b** upon reaction with the sugars (1-O-methyl-2-deoxy-D-ribose > 2-deoxy-D-ribose ≥ D-ribose) is similar to those found in a previous study on the reactivity of charged phenyl monoradicals toward these same sugars [4a]. In this previous study, the trend was explained by using enthalpy calculations that suggested that hydrogen atom abstraction from multiple sites in 1-O-methyl-2-deoxy-D-ribose is about 1.5 kcal/mol more exothermic

than for either D-ribose or 2-deoxy-D-ribose. There is every reason to believe that the same applies to the reactions of the biradicals **1a** and **1b**. The observed reactivity is discussed below in terms of the S-T gaps and EAs of the biradicals.

Singlet-Triplet Gaps

Computational studies [8] have suggested that the S-T gaps of σ,σ -biradicals with singlet ground states correlate inversely with the efficiencies for hydrogen atom abstraction. In order for a singlet biradical to undergo a radical reaction, there is a need to uncouple the two biradical electrons in the transition state. As the S-T gap increases, the energy that is required to uncouple the electrons increases, which increases the energy of the transition state, thereby reducing radical reactivity. The calculated S-T gap ordering of the biradicals that react via radical pathways, **1a** ≈ **1b** < **2a** ≈ **2b** (Table 1), does correlate to some extent with the inverse of the overall reaction efficiency ordering (**1a** > **1b** > **2a** > **2b**) for the sugars studied (Tables 2 and 3).

Interestingly, biradicals **1a** and **1b** react with all the sugars by hydrogen atom abstraction with efficiencies greater than those of the analogous monoradicals **4a** and **4b**, respectively. A rationale for this

Scheme 4

Figure 1. A mass spectrum measured after one second for the reaction of 4,6-didehydroisoquinolinium ion (**1a**) with D-ribose at a nominal pressure of 2×10^{-9} torr. The peak at m/z 128 is due to **1a**, while the peaks at m/z 129 and m/z 130 are due to a primary and secondary hydrogen atom abstraction, respectively, by **1a** from D-ribose.

finding is presented in the next section. Furthermore, biradicals **2b** and **3b**, unlike **2a** and **3a**, do not react with any of the sugars studied, despite the similarities in the S-T gaps of **2a** and **2b**, and **3a** and **3b**. This

observation, and the anomalous reaction efficiencies observed for **1a** and **1b**, suggest that other factors besides the S-T gap may be influencing the rates of these reactions.

Figure 2. A mass spectrum measured after twenty seconds for the reaction of 5,8-didehydroisoquinolinium ion (**2a**) with D-ribose at a nominal pressure of 8×10^{-9} torr. The peak at m/z 128 is due to **2a**, while the peak at m/z 278 is due to a stable adduct of **2a** and D-ribose (one possible structure shown).

Figure 3. A mass spectrum measured after twenty seconds for the reaction of 5,7-didehydroquinolinium ion (**3a**) with D-ribose at a nominal pressure of 2.7×10^{-8} torr. The peak at m/z 128 is due to **3a**, while the peak at m/z 278 is due to a stable adduct of **3a** and D-ribose (one possible structure shown).

Figure 4. A mass spectrum measured after one second for the reaction of 4-dehydroisoquinolinium ion (**4a**) with D-ribose at a nominal pressure of 2×10^{-9} torr. The peak at m/z 129 is due to **4a**, while the peak at m/z 130 is due to hydrogen atom abstraction by **4a** from D-ribose.

Polar Effects

Polarization of the transition state has long been known to influence the reactivity of electrophilic and nucleophilic monoradicals, i.e., the more polar the transition state, the lower its energy, and consequently, the faster the reaction. Several models for predicting barrier heights for radical/molecule reactions have been developed over the years. The ionic avoided curve crossing model [24] has been used previously [6] to explain radical reactivity such as that reported here. This model (which is a slightly modified version of the valence-bond avoided curve-crossing model [25] developed by Shaik et al.) defines the barrier height of a radical/molecule reaction based on an avoided crossing of the ground state and some hypothetical ionic excited state (instead of the triplet state proposed by Shaik et al.). This model was developed based on the computational finding that the transition state energy for hydrogen atom abstraction by several radicals (e.g., OH and Br) correlates directly with the ionic energy of the separated reactants, which is expressed as the difference (ΔR) in the ionization energy (IE) and electron affinity (EA) of the reactants. For a positively charged radical, $R^+Z^\bullet$, and neutral reagent, XH, the important ionic resonance structure of the transition state can be represented as $[R^+Z^-][XH^+^\bullet]$ [24, 26, 27]. Increasing the EA of the radical or decreasing the IE of the neutral reagent stabilizes this configuration [26–28].

However, little is known about polar effects in the reactions of biradicals. It was demonstrated in a recent study [11] that as the EA of a biradical increases, the overall reaction efficiency increases for reactions with simple organic substrates. The ordering of the EAs for the biradicals studied here ($1a > 1b > 2a > 2b > 3a > 3b$; Table 1) correlates to some extent with the relative reaction efficiencies for the sugars. For example, the reaction efficiencies of 2-deoxy-D-ribose are 46%, 32%, 0.70%, 0%, 0.43%, and 0%, respectively. This finding is in agreement with a previous study on reactions of phenyl monoradicals with sugars [4a]; in this study, the reaction efficiency was found to increase as the EA of the radical increased.

Both biradicals **1a** and **1b** react at efficiencies higher than those of the analogous monoradicals **4a** and **4b** (Tables 2 and 3). This finding can be explained by the greater (calculated) EA of **1a** compared with **4a** (5.99 and 5.72 eV, respectively) and of **1b** compared with **4b** (5.82 and 5.55 eV, respectively). The importance of the EA is even more evident when comparing the reactivities of biradicals **1a–3a** with **1b–3b** (Tables 2 and 3). For example, **1a** and **1b** have similar (calculated) S-T gaps but different EAs (5.99 and 5.82 eV, respectively). This results in very different reactivity: **1a** reacts about 1.5 times faster than **1b** with all of the sugars. A similar effect was observed for **2a** and **2b** (EAs: 5.73 and 5.59 eV, respectively).

The IEs of the sugars are the same within experimental

error (9.1 eV for D-ribose and 9.0 eV for both 2-deoxy-D-ribose and 1-O-methyl-2-deoxy-D-ribose) [4a]. Therefore, any given biradical would be expected to react at a similar rate with all of the sugars based on the ionic avoided curve crossing model discussed above. This was not the case. For example, biradical **1a** abstracts hydrogen atoms from 1-O-methyl-2-deoxy-D-ribose much faster than from 2-deoxy-D-ribose (56% and 46%, respectively). The difference in reaction rates may be explained by previous enthalpy calculations [4a] that suggested that hydrogen atom abstraction from multiple sites in 1-O-methyl-2-deoxy-D-ribose is more exothermic than for either D-ribose or 2-deoxy-D-ribose.

Conclusions

The work reported here represents the first study on the reactivity of σ,σ -biradicals toward sugars. The biradicals with small S-T gaps (weak spin-spin coupling) react via hydrogen atom abstraction with all of the sugars studied. However, the biradicals with large S-T gaps (e.g., *meta*-benzynes analogs) are either unreactive or react via (nonradical) addition pathways. Thus, not all σ,σ -biradicals may be able to damage DNA by hydrogen atom abstraction. The biradicals with intermediate S-T gaps (e.g., *para*-benzynes analogs) abstract hydrogen atoms very slowly, and only from two of the sugars studied here. This result suggests that *para*-benzynes analogs may be able to damage DNA more selectively than biradicals that have smaller S-T gaps. The observed trend in the overall reaction efficiencies, $1 > 2 > 3$ (for any given sugar), is in agreement with the inverse ordering of the (calculated) S-T gaps as well as the direct ordering of the (calculated) EAs. The relative reactivities of biradicals having similar S-T gaps are controlled by their relative EAs. In fact, the radical-reactivity hindering effect of the S-T gap can be counterbalanced by a high electrophilicity (large EA). The influence of the EA is so strong that biradicals **1a** and **1b** abstract hydrogen atoms at substantially higher efficiencies than the related monoradicals **4a** and **4b**, respectively. Thus, the same factors that control the reactivities of these biradicals toward simple organic substrates (e.g., S-T gap and EA) also control their reactivities toward sugars.

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