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Effects of Hydrogen Bonding on the Gas-phase Reactivity of Didehydroisoquinolinium Cation Isomers

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Two previously unreported isomeric biradicals with a 1,4-radical topology, the 1,5-didehydroisoquinolinium cation and the 4,8-didehydroisoquinolinium cation, and an additional, previously reported isomer, the 4,5-didehydroisoquinolinium cation, were studied to examine the importance of the exact location of the radical sites on their reactivities in the gas phase. The experimental results suggest that hydrogen bonding in the transition state enhances the reactivity of the 1,5-didehydroisoquinolinium cation towards tetrahydrofuran but not towards allyl iodide, dimethyl disulfide or *tert*-butyl isocyanide. The observation of no such enhancement of reactivity towards tetrahydrofuran for the 4,8-didehydroisoquinolinium and 4,5-didehydroisoquinolinium cations supports this hypothesis as these two biradicals are not able to engage in hydrogen bonding in their transition states for hydrogen atom abstraction from tetrahydrofuran. Quantum chemical transition state calculations indicate that abstraction of a hydrogen atom from tetrahydrofuran by the 1,5-didehydroisoquinolinium cation occurs at the C-1 radical site and that the transition state is stabilized by hydrogen bonding.

Introduction

Didehydroarenes, aromatic carbon-centered σ,σ-biradicals, have received intense attention since the discovery that 1,4-didehydroarenes and analogs are the biologically active intermediates of the enediyne class of antitumor antibiotics.[1–3] Gas-phase studies on related charged molecules (that can be studied using mass spectrometers) have offered valuable insights into the reactivities of these elusive species.[4-9] These studies have suggested that the reactivity of the biradicals depends on the magnitude of the (calculated) vertical electron affinity (EA) of their radical sites, their (calculated) singlet-triplet splitting (ΔE_{S-T}), and their (calculated) distortion energy if they are *meta*-benzyne analogs.[7–9] However, the importance of the exact location of the radical sites in isomers with the same radical topology has not been explored.

Herein we report a study on the reactivities of two previously unreported, isomeric biradicals with a 1,4-radical topology, the 1,5-didehydroisoquinolinium cation **6** and the 4,8-didehydroisoquinolinium cation **7**, and compare their behavior to that of an earlier reported[10] isomer, the 4,5-didehydroisoquinolinium cation **5**, as well as related monoradicals (Figure 1).

Figure 1. The dehydro- and didehydroisoquinolinium cations studied.

Results and discussion

The three isomeric biradicals and their monoradical analogs were generated from iodo- and/or nitroprecursors in a dual-cell Fourier-transform ion cyclotron resonance mass spectrometer via protonation followed by cleavage of the iodine atoms and/or nitro groups via collision-activated dissociation, as described previously.[4-6,9] The radicals were isolated and transferred into a clean cell for reactivity studies. The reactivities of the different radicals toward each reagent are compared below.

Based on the literature, organic singlet ground-state biradicals of the type of interest here may be expected to display similar reactivity if they have similar EAs and S-T splittings (with the exception of *meta*-benzyne analogs).[4,8,9,11] However, in this study, biradical **6** was found to abstract a hydrogen atom from tetrahydrofuran (THF) substantially faster than biradical **7** (reaction efficiencies: 68% and 10%, respectively) despite having a similar (calculated)[12,13] EA and S-T splitting. In sharp contrast, both biradicals abstract an iodine atom from allyl iodide at a similar efficiency (54% and 41%, respectively). To rationalize these findings, the reactivities of
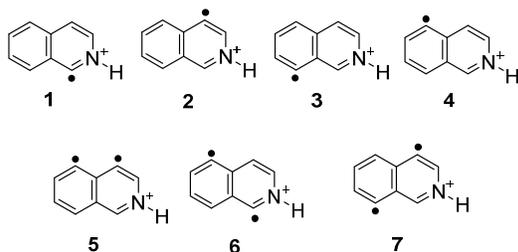
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biradicals **5**-**7** and related monoradicals **1**-**4** are discussed in detail below.

The reactivity of the monoradicals is straightforward. The 1-dehydroisoquinolinium cation (**1**), 4-dehydroisoquinolinium cation[10] (**2**), 8-dehydroisoquinolinium cation (**3**) and 5-dehydroisoquinolinium cation[10] (**4**) react predominantly by abstraction of a hydrogen atom from THF, an iodine atom from allyl iodide, an SCH_3 group from dimethyl disulfide (DMDS) and CN and HCN groups from *tert*-butyl isocyanide (*t*-BuNC), as expected[4,14] (Table 1). The reactivities of the monoradicals reflect their (calculated) EAs, also as expected.[15] Monoradical **1** is the most reactive, followed by **2**, **3** and **4** (calculated EAs are as follows: **1**: 6.45 eV; **2**: 5.76 eV; **3**: 5.16 eV; **4**: 4.98 eV; Table 1).

The reactivity of a given monoradical toward different reagents depends on several variables, including the ionization energy of the reagent and the reaction mechanism.[16,17] Based on the literature, the efficiencies of reactions of the monoradicals studied here with THF are expected to be lower than with allyl iodide, DMDS, and *t*-BuNC.[16] This was observed for **2**, **3** and **4**. However, monoradical **1** exhibits comparable reactivity toward THF as toward the other reagents (reaction efficiencies: THF: 83%; allyl iodide: 73%; DMDS: 87%; *t*-BuNC: 100%; Table 1). This observation can be rationalized by a stabilizing hydrogen bonding interaction in the transition state for hydrogen atom abstraction from THF, as reported earlier.[18] This effect is only possible for **1** since only this radical has a radical site on the carbon atom adjacent to the protonated nitrogen atom, which enables THF to engage in hydrogen bonding with the NH^+ proton in the transition state.

The reactions of biradicals **6** and **7** with all studied reagents mostly yield primary product ions analogous to those of the four related monoradicals. They also yield secondary product ions not observed for the monoradicals (Tables 1 and 2) due to radical reactions at the second radical site. These reactions are analogous to those occurring at the most reactive radical site of the biradicals and to those observed for the monoradicals. For example, two consecutive hydrogen atom abstractions from THF, two consecutive iodine atom abstractions from allyl iodide, two consecutive SCH_3 group abstractions from DMDS and two consecutive CN group abstractions from *t*-BuNC were observed (Table 2)**.** The proposed mechanisms for the dominant reactions of biradical **7** with allyl iodide are shown in Scheme 1.

Biradical **6** has a greater (calculated) EA than **7** (**6**: 6.22 eV; **7**: 5.69 eV), while their (calculated) S-T splittings are similar (**6**: -8.9 kcal mol^{-1}; **7**: -7.6 kcal mol^{-1}; Table 2), which suggests greater reactivity for **6** than **7**. This was observed for all four of the neutral reagents studied here: THF, DMDS, *t*-BuNC and allyl iodide (Table 2).

Most of the reactions of **6** and **7** with DMDS, *t*-BuNC and allyl iodide were also observed for a previously reported[10]

biradical **5.** The reaction efficiencies of **5** are similar to those of **6** and slightly greater than those of **7** toward these three reagents

Scheme 1. Proposed stepwise mechanisms for iodine atom abstraction followed by iodine atom or allyl group abstraction from two allyl iodide molecules by biradical **7**.

(with the exception of *t*-BuNC because this reagent is basic enough to rapidly deprotonate **6** but not **5** or **7**). Biradical **5** has a relatively small (calculated) S-T splitting (-1.1 kcal mol^{-1}; Table 2), which is expected to make it more reactive than **6** and **7**, but it has a lower EA than **6** and an EA comparable to that for **7**. The reaction efficiencies measured for **5**, **6** and **7** (for allyl iodide: 41%, 42%, and 54%; for DMDS: 48%, 62%, and 75%, respectively; Table 2) suggest that the greater EA of **6** partially counteracts the rate enhancing effect of the small S-T splitting of **5**.

A deviation from above reactivity trends was revealed by the high efficiency at which **6** reacts with THF (efficiencies of **6**, **7** and **5** are 68%, 10%, and 27%, respectively; Table 2). This may be explained by a stabilizing hydrogen bonding interaction in the transition state for reaction of **6** with THF. Biradical **6** is the only biradical among the ones studied here that is capable of hydrogen bonding in the transition state, due to the short distance between the C-1 radical site and the protonated nitrogen atom, the only site capable of hydrogen bonding with the oxygen atom of THF (Scheme 2). Similar behavior was discussed above for monoradical **1**. As observed for monoradical **1**, biradical **6** reacts with THF at a comparable efficiency as with the other reagents (Table 2), which is not the case for monoradicals **2** - **4** or biradicals **5** and **7**. Furthermore, transition state calculations carried out for **6** support the hypothesis that hydrogen bonding stabilizes the transition state for the abstraction of the first hydrogen atom from THF by the C-1 radical site (Figure 2). The activation enthalpy and the enthalpy of reaction were calculated to be -15.0 kcal mol^{-1} and -21.9 kcal mol^{-1}, respectively. To the best of our knowledge, this is the first time that hydrogen bonding has
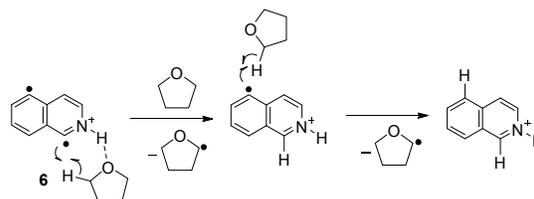
been observed to influence the reactivity of a biradical.

Scheme 2. Proposed stepwise mechanisms for hydrogen atom abstraction reactions from two THF molecules by biradical **6**.
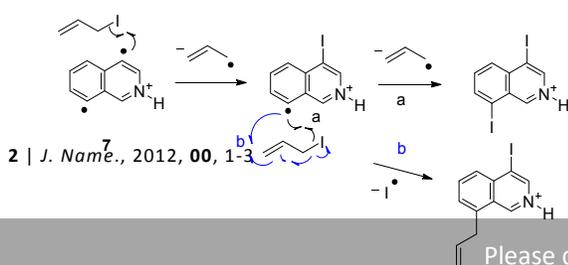
Table 1. Reaction Efficiencies[a] and Product Branching Ratios[b,c] for Reactions of Monoradicals **1–4** with Various Reagents, and The Calculated Vertical Electron Affinities[d] (EA) of the Radicals

Reagents → Radical ↓	THF	allyl iodide	S-S	NC			
1 EA = 6.45 eV	H abs[c] **100%**	I abs **94%** C₃H₅ abs **6%**	SCH₃ abs **100%**	CN abs **96%** HCN abs **4%**
	Efficiency = 83%	Efficiency = 73%	Efficiency = 87%	Efficiency = 100%
2 EA = 5.76 eV	H abs **100%**	I abs **94%** C₃H₅ abs **6%**	SCH₃ abs **100%**	CN abs **96%** HCN abs **4%**
	Efficiency = 39%	Efficiency = 71%	Efficiency = 73%	Efficiency = 84%
3 EA = 5.16 eV	H abs **100%**	I abs **100%**	SCH₃ abs **100%**	CN abs **94%** HCN abs **6%**
	Efficiency = 25%	Efficiency = 43%	Efficiency = 34%	Efficiency = 68%
4 EA = 4.98 eV	H abs **100%**	I abs **98%** C₃H₅ abs **2%**	SCH₃ abs **100%**	CN abs **94%** HCN abs **6%**
	Efficiency = 8%	Efficiency = 36%	Efficiency = 48%	Efficiency = 63%

[a] Reaction efficiencies (Efficiency) are reported as $k_{reaction}/k_{collision} \times 100$. [b] Branching ratios for primary products. [c] abs = abstraction.

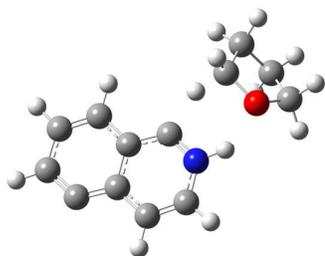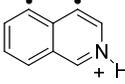[d] Calculated at the CASPT2/CASSCF(12,11)/cc-pVTZ//CASPT2/CASSCF(11,11)/cc-pVTZ level of theory.

Figure 2. Transition state calculated for hydrogen atom abstraction from THF by the C-1 radical site in **6** (UB3LYP/cc-pVTZ//UB3LYP/cc-pVTZ level of theory).

Conclusions

The isomeric biradicals **5**, **6** and **7** studied here were found to undergo two radical reactions with all reagents, as expected. Their product distributions and reaction efficiencies are similar, with the exception of one reagent - THF. The much higher efficiency of reactions of **6** with THF, compared to the efficiencies of **5** and **7**, is likely due to a stabilizing hydrogen bonding interaction that **6** can have with THF in the transition state for hydrogen atom abstraction. This result indicates that the possibility of *stabilizing hydrogen bonding in a transition state* must be taken into account when considering reactivities of biradicals capable of forming a hydrogen bond. When hydrogen bonding is not the reactivity controlling factor, the *EA*

and S-T splitting appear to be the principal factors affecting the reactivity of isomeric biradicals. Finally,

the reaction efficiencies of the 1- and 4-dehydroisoquinolinium cations (i.e.,

Table 2. Reaction Efficiencies[a] and Product Branching Ratios[b,c] for Reactions of Biradicals **5–7** with Various Reagents, and Calculated Vertical Electron Affinities[d] (EA) and Singlet-Triplet Splittings[e] (ΔE_{ST})

Reagents / Radical	(THF)	(allyl iodide)	(S–S)	(NC)
5 EA = 5.77 eV ΔE_{ST} = -1.1 kcal mol^{-1}	2 x H abs[e] **40%** H abs **14%** (2º) H abs CH_2O abs **25%** H_2O abs **6%** C_2H_4 abs **6%** H$^-$ abs **5%** C_3H_3 abs **2%** C_2H_4O abs **1%** C_3H_6 abs **1%**	I abs **58%** (2º) I abs (2º) C_3H_5 abs C_3H_4 abs **42%**	SCH_3 abs **51%** (2º) SCH_3 abs SCH_2 abs **31%** $HSCH_3$ **18%**	HCN abs **70%** CN abs **30%** (2º) CN abs (2º) HCN abs (2º) Addition
	Efficiency = 27%[f]	**Efficiency = 42%[g]**	**Efficiency = 62%[h]**	**Efficiency = 55%[i]**
6 EA = 6.22 eV ΔE_{ST} = -8.9 kcal mol^{-1}	H abs **50%** (2º) H abs CH_2O abs **13%** 2 x H abs **9%** H$^-$ abs **8%** C_2H_4 abs **7%** H_2O abs **4%** H +CH_2O abs **3%** 2H + CH_2 abs **2%** Addition **1%** C_3H_6 abs **1%** C_2H_4O abs **1%** C_3H_3 abs **1%**	I abs **83%** (2º) I abs (2º) C_3H_5 abs C_3H_5 abs **11%** (2º) I abs C_3H_4 abs **6%**	SCH_3 abs **89%** (2º) SCH_3 abs $SSCH_3$ **6%** $HSCH_3$ **4%** SCH_2 abs **1%**	HCN abs **39%** CN abs **32%** (2º) CN abs (2º) HCN abs (2º) Addition H$^+$ transfer **29%**
	Efficiency = 68%[k]	**Efficiency = 54%[l]**	**Efficiency = 75%[m]**	**Efficiency = 96%[n]**
7 EA = 5.69 eV ΔE_{ST} = -7.6 kcal mol^{-1}	H abs **35%** (2º) H abs 2 x H abs **33%** C_2H_4 abs **10%** H$^-$ abs **6%** C_3H_3 abs **4%** CH_2O abs **4%** H + CH_2 abs **4%** C_3H_6 abs **2%** 2H + CH_2 abs **1%** C_3H_5 abs **1%**	I abs **92%** (2º) I abs (2º) C_3H_5 abs C_3H_4 abs **8%**	SCH_3 abs **88%** (2º) SCH_3 abs SCH_2 abs **7%** $HSCH_3$ abs **5%**	HCN abs **62%** (2º) HCN abs (2º) C_5H_9N abs CN abs **38%** (2º) CN abs (2º) HCN abs (2º) C_5H_9N abs (2º) Addition
	Efficiency = 10%	**Efficiency = 41%[p]**	**Efficiency = 48%[q]**	**Efficiency = 41%**
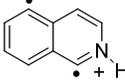
[a] Reaction efficiencies (Efficiency) are reported as $k_{reaction}/k_{collision} \times 100$. The precision of the measured efficiencies is $\pm10\%$. [b] Primary products' branching ratios; secondary products are noted as (2°) and are listed under the primary products that produce them. [c] abs = abstraction. [d] Vertical electron affinities calculated at the CASPT2/CASSCF(13,12)/cc-pVTZ//CASPT2/CASSCF(12,12)/cc-pVTZ level of theory. [e] Singlet-triplet splittings calculated at the CASPT2/CASSCF(12,12)/cc-pVTZ//CASPT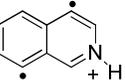2/CASSCF(12,12)/cc-pVTZ level of theory. Note that a negative value means that the singlet state lies energetically below the triplet state. Zero-point energies and 298 K thermal contributions were derived from the (unscaled) UB3LYP/cc-pVTZ//UB3LYP/cc-pVTZ frequencies. [f] From non-linear curve fit (least squares non-linear fit of the pseudo-first order plot), 25% of the reactant ion population is unreactive. [g] Same as f but 47%. [h] Same as f but 43%. [i] Same as f but 13%. [j] Same as f but 44%. [k] Same as f but 13%. [l] Same as f but 16%. [m] Same as f but 15%. [n] Same as f but 20%. [o] Same as f but 19%. [p] Same as f but 63%. [q] Same as f but 64%.

monoradicals **1** and **2**) are systematically greater than those of the biradicals with a radical site at C-1 or C-4 in spite of the fact that the biradicals have equal or greater calculated EAs. This is true even for **5** with a relatively small calculated S-T splitting (-1.1 kcal/mol). Therefore, *coupling between the radical sites*, *even when very weak*, *lowers the reactivity of the biradicals compared to monoradicals*.

As the dependence of the reactivity on the exact location of the radical sites in isomeric biradicals with the same radical topology has not been explored until now, the findings described above greatly improve the understanding of the chemical properties of organic biradicals. Further, the finding of the importance of hydrogen bonding capability for the hydrogen atom abstraction efficiency of a biradical implies that biradical intermediates that are capable of forming a hydrogen bond near one or both of the radical sites are likely to cleave DNA more efficiently than biradicals without this capability.

Conflicts of interest

There are no conflicts to declare.

Experimental

Materials and methods

All experiments were carried out in a Finnigan FTMS 2001 dual-cell FT-ICR mass spectrometer. The mono- and biradicals **1-4** and **6-7** (Table 1) were generated in one cell by using previously reported methods.[14,19] Briefly, the nitro- and/or iodoprecursors of the radicals were introduced into one side of the dual-cell ion trap of the mass spectrometer via a heated solids probe, ionized by protonation, and isolated by ejecting all other ions from the ion trap. The ionized precursors were then transferred into the other, clean cell, followed by sustained off-resonance irradiated collision-activated dissociation[20] (SORI-CAD) to homolytically cleave C-I and/or C-NO$_2$ bonds of the protonated precursors. The (bi)radicals were isolated and allowed to react with tetrahydrofuran (THF), allyl iodide (AI), dimethyl disulfide (DMDS) and *tert*-butyl isocyanide (*t*-BuNC) for varying periods of time. The second-order reaction rate constants (k_{exp}) and reaction efficiencies ($k_{reaction}/k_{coll}$) were determined as described in the literature.[4,21-24] The absolute values are estimated to be accurate only within ±50% but the relative values are much more accurate (±10%). The product branching ratios were determined by dividing the abundance of each primary reaction product ion by the sum of all primary reaction product abundances.

Synthetic procedures

The precursor for monoradical **4,** 5-nitroisoquinoline, was purchased from Sigma-Aldrich and used without further purification. The precursors for monoradical **1**, 1-iodoisoquinoline,[25] and monoradical **2**, 4-iodoisoquinoline,[26] were synthesized by known methods. The precursors for biradical **5**, 4-iodo-5-nitroisoquinoline,[10] and biradical **7**, 4-iodo-8-nitroisoquinoline,[27] were also synthesized by known methods.

The precursor for monoradical **3**, 8-iodoisoquinoline, was synthesized by dissolving (0.5 g, 3.36 mmol) 8-aminoiso-quinoline (Carbocore) in a mixture of concentrated HCl (3 mL) and H$_2$O (3 mL) cooled in an ice/salt bath and slowly adding a solution of NaNO$_2$ (0.28 g, 4.03 mmol) in H$_2$O (2 mL), to give a red solution. This solution was stirred for 15 min, and a solution of KI (1.12 g, 6.73 mmol) in H$_2$O (3 mL) was added to it. The mixture was heated for 3 hr at 100˚C, and then cooled and basified with aqueous NH$_3$. The product was extracted with dichloromethane and the organic layer washed with 5% sodium metabisulfide followed by a brine solution, then dried and chromatographed on silica gel, eluting with CH$_2$Cl$_2$:MeOH (95:5), to give 8-iodoisoquinoline (0.52 g, 60%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 (t, J = 7.9 Hz, 1H), 7.44 (d, J = 5.6 Hz, 1H), 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 (s, 1H). ESI MS: [M+H]$^+$ m/z 256.

The precursor for biradical **6**, 1-iodo-5-nitroisoquinoline, was synthesized by dissolving (1.50 g, 9.65 mmol) 1-chloroisoquinoline (Carbocore) in cooled (0˚C) concentrated H$_2$SO$_4$ (20 mL), which turned the solution yellow. An excess of concentrated HNO$_3$ (2 mL) was added to the stirred solution and a change of color to orange was observed. The solution was stirred at 0˚C for 5 min, then allowed to warm up to room temperature and stirred for 30 min more. The solution was poured onto ice, turning the mixture to a creamy yellow color. The solution was basified to pH 8, filtered and dried to give yellow crystals. The products were separated by chromatography. Two products were obtained, 1-chloro-5-nitroisoquinoline (70% yield) and 1-chloro-8-nitroisoquinoline (10% yield).

1-Iodo-5-nitroisoquinoline **6** was synthesized for the first time from 1-chloro-5-nitroisoquinoline by following the procedure described by Wolf,[25] in which the chlorine atom was exchanged with an iodine atom (yield 80%). The halogen exchange was verified by mass spectrometry that revealed the absence of 1-chloro-5-nitroisoquinoline ([M+H]$^+$ m/z 209). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 (t, J = 8.0 Hz, 1H), 8.38 (d, J = 6.1 Hz, 1H), 8.47 (d, J = 6.1 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.58 (d, J = 3.4 Hz, 1H). ESI MS: [M+H]$^+$ m/z 301. The structure was also verified by x-ray crystallography.

Computational methods

Molecular geometries for all species were optimized at the multiconfigurational self-consistent field (MCSCF) and density functional (DFT) levels of theory by using the correlation-consistent polarized valence-triple-ζ (cc-pVTZ) basis set.[28] The MCSCF calculations were of the complete active space (CASSCF) variety[29] and included (in the active space) the full π-space for each molecule and, for each of the mono- and biradicals, the nonbonding σ

orbital(s). The DFT calculations used the gradient-corrected exchange functional of Becke,[30] which was combined with the gradient-corrected correlation functional of Lee, Yang and Parr[31] (B3LYP). 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 the mono- and biradicals employed an unrestricted formalism.

To improve the molecular orbital calculations, dynamic electron correlation was also accounted for by using multi-reference second-order perturbation theory[32,33] (CASPT2) for multi-configurational self-consistent field (MCSCF) reference wave functions; these calculations were carried out for the MCSCF optimized geometries. 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.[34] Thus, the electronic energies are of the CASPT2/CASSCF(m,n)/cc-pVTZ//CASSCF(m,n)/cc-pVTZ variety (where m is the number of active electrons and n is the number of active orbitals), and estimates of the thermodynamic quantities, E_0 and H_{298}, are derived by adding to these electronic energies ZPVE and the sum of ZPVE and ($H_{298} - E_0$), respectively, where the latter are derived from the DFT calculations.

In order to compute vertical electron affinities (EA$_v$) for the mono- and biradicals, single-point calculations (CASPT2/CASSCF(m,n)/cc-pVTZ), using the CASSCF(m,n)/cc-pVTZ optimized geometry for each radical, 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.[35] Thus, for the monoradicals (doublet ground states), these calculations were carried out for (zwitterionic) *singlet* states, whereas for the biradicals (singlet ground states), calculations were carried out for (zwitterionic) *doublet* states.[36]

All CASPT2/MCSCF and DFT calculations were carried out with the MOLCAS 8.0[37] and Gaussian 09[38] electronic structure program suites, respectively.

Acknowledgements

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