Variations on the Bergman Cyclization Theme:
Electrocyclizations of Penta–, Hepta– and Octa–diynes

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Several novel anti-tumor pharmaceuticals have been developed that leverage the *in vivo* production of the aromatic *p*-benzyne diradical via Bergman cyclization of (Z)-hexa-3-ene-1,5-diyne derivatives to initiate lysis in cancer cells and halt tumor growth. To expand the pharmacological toolkit for leveraging this chemistry in a wider range of anti-tumor applications, we have examined Bergman-type electrocyclizations of 5-, 7-, and 8-membered ionic pseudo-enediyne precursors using high-level *ab initio* electronic structure theory. We have characterized the energetics of these electrocyclizations using spin-flip formulations of equation-of-motion coupled cluster theory with single and double substitutions (SF-EOM-CCSD) and time-dependent density functional theory with the "50/50" functional [SF-TDDFT(50/50)], as well as quantifying the aromaticity of the diradical products of these electrocyclizations with the nucleus-independent chemical shift (NICS) approach. We find that, while the 5-membered precursor yields a cyclic diradical product, the barrier of nearly +70 kcal/mol prevents this cyclization from being a reasonable experimental target. Furthermore, despite the barriers for the cyclizations of the 7- and 8-membered precursors being much more amenable to reaction *in vivo*, we find that the cyclic diradicals undergo bicyclization on the singlet surface and a loss of diradical character which could neutralize their anti-tumor activity. Finally, when comparing our findings to the literature on the canonical Bergman cyclization, we find that both internal strain energy and aromaticity play a stabilizing role for the cyclic diradical products of these reactions. These findings showcase the delicate balance between (i) a reduction in the barrier to cyclization and (ii) the likelihood of subsequent radical elimination in a more flexible cyclic diradical resulting from expanding the overall chain length of pseudo-enediyine precursors in Bergman-type electrocyclizations. Further development of novel anti-tumor therapeutics leveraging this chemistry must therefore carefully consider this behavior to ensure the viability of the cyclic diradical products for encouraging lysis in cancer cells.