



Enediynes, enyne-allenes, their reactions, and beyond

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Enediynes undergo a Bergman cyclization reaction to form the labile 1,4-didehydrobenzene (*p*-benzyne) biradical. The energetics of this reaction and the related Schreiner–Pascal reaction as well as that of the Myers–Saito and Schmittel reactions of enyne-allenes are discussed on the basis of a variety of quantum chemical and available experimental results. The computational investigation of enediynes has been beneficial for both experimentalists and theoreticians because it has led to new synthetic challenges and new computational methodologies. The accurate description of biradicals has been one of the results of this mutual fertilization. Other results have been the computer-assisted drug design of new antitumor antibiotics based on the biological activity of natural enediynes, the investigation of hetero- and metallo-enediynes, the use of enediynes in chemical synthesis and materials science, or an understanding of catalyzed enediyne reactions. © 2013 John Wiley & Sons, Ltd.

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INTRODUCTION

A review on the enediynes is necessarily an account of intense and successful interdisciplinary interactions of very different fields in chemistry involving among others organic chemistry, matrix isolation spectroscopy, quantum chemistry, biochemistry, natural product synthesis, drug design, medicinal chemistry, transition metal chemistry, or materials science. The roots of the enediyne chemistry can be found in a 1972 communication of Jones and Bergman in the *J. Am. Chem. Soc.*, in which the cyclization of (*Z*)-hex-3-ene-1,5-diyne (the parent enediyne of **1** in Figure 1) is described and evidence for the intermediate formation of the labile 1,4-didehydrobenzene (*p*-benzyne) provided (see **2** in Figure 1).¹ Already 1 year later, Bergman² published a review article on *Reactive 1,4-didehydroaromatics* because the work of the previous year related to the hot topics of the early 1970s: (i) the energetics of

symmetry-allowed pericyclic reactions, (ii) aromaticity as a driving force for chemical reactions, and (iii) the investigation of labile intermediates with biradical character. The henceforth called Bergman cyclization provided deeper insight into the electronic structure of biradical intermediates, the mechanism of organic reactions, and orbital symmetry rules. Remarkable in this connection is that Bergman already derived in his review article reasonable energetics of the reaction on the basis of empirical considerations, decided for a biradical as the most likely electronic structure of *p*-benzyne (in view of the trapping products, which also confirmed its existence as an intermediate), and related the cyclization reaction to observations Masamune and co-workers³ had made for cyclic enediynes also in the year 1972. These authors had obtained products that suggested the intermediacy of didehydronaphthalene and 9,10-didehydroanthracene biradicals. In summary, several of the topics, which became relevant in enediyne research much later, are already contained in the 1973 review article of Bergman.²

Enediyne chemistry had a strong impact on a number of fields where quantum chemistry should be mentioned first. The *p*-benzyne was the first non-trivial biradical, for which, in view of the lack of experimental data, a reliable quantum chemical

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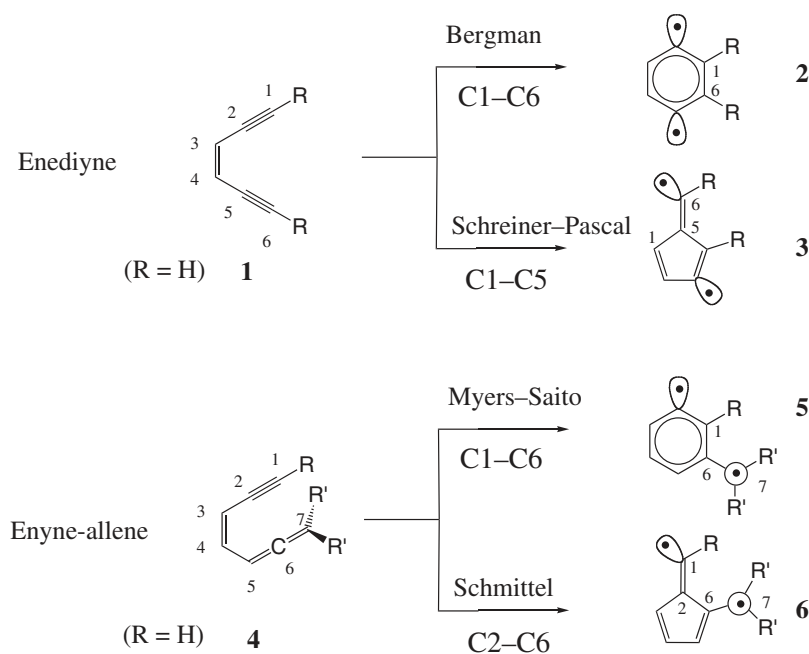


FIGURE 1 | Bergman, Schreiner–Pascal, Myers–Saito, and Schmittel reaction of enediyne and enyne-allenes.

description was needed. This need was enhanced by the discovery of natural enediyne in the 1980s.^{4–6} The natural enediyne calicheamicin (1987),⁵ esparamicin (1987),⁶ and dynemicin (1990)⁷ were soon after their discovery in the years 1987 and 1990 considered as possible leads for antitumor antibiotics where this hope was based on their relationship to neocarzinostatin.⁸ The latter compound had already been discovered in 1965,⁹ and its biological activity was early known. Neocarzinostatin can be considered as an enediyne with an epoxidized double bond, and therefore its biological activity was related to a Bergman-type cyclization of an intermediate enyne-cumulene.¹⁰ Hence, the discovery of the natural enediyne and their chemistry established the importance of the cycloaromatization reaction discovered by Jones, Bergman, and Masamune in the early 1970s.

The Bergman reaction may be formally classified as an electrocyclic reaction.¹¹ However, it has to be mentioned that for an electrocyclic reaction, the 6π system orthogonal to the symmetry plane of **1** should be directly involved in the formation of the new CC bond, which is not the case. Other authors have related the Bergman reaction to the Cope rearrangement and speak of a *formal Cope rearrangement*.^{12,13} Again, this can be questioned when considering just the Bergman reaction whereas the Bergman and retro-Bergman reaction seen together (i.e., considering both the formation of bond C1C6 to give **2** and the cleavage of bond C3C4 in **2**) may be formally seen in

this way (interaction of two in-plane ally radicals) although this would lead to the transition state of the Cope rearrangement being identical to the intermediate *p*-benzyne biradical. In this situation, it is appropriate to follow the suggestion of Alabugin and co-workers¹⁴ and to speak in the case of the Bergman and Myers–Saito rearrangements (Figure 1) of cycloaromatization reactions as a special class of ring-forming reactions.

The correct description of a singlet biradical such as *p*-benzyne requires a methodology, which was not available in the 1970s, however came into general use with the availability of coupled cluster methods¹⁵ and perturbation theory corrected complete active space methods in the late 1980s and early 1990s, respectively.¹⁶ A correct quantum chemical description of the Bergman cyclization implies more than just a reliable description of an organic biradical. It requires a balanced account of nondynamic (multireference) electron correlation effects (for the biradical) and dynamic electron correlation effects (especially including three-electron effects for the correct account of different types of electron delocalization in reactant and product). Even in the year 2013, this problem cannot be considered to be fully solved for the Bergman and the Bergman-related reactions (Figure 1) in the way that larger enediyne and enyne-allenes can be easily investigated.

In this situation, quantum chemists focused on the possibilities of density functional theory (DFT),¹⁷

which could be easily applied to larger systems and did not suffer as strongly as wave function theory from the basis set truncation error. It is fair to say that the study of enediyne and their reactions has led to a better understanding of DFT as well as to the development of new DFT methods with multireference character. Hence, a review on enediyne has to sketch the close connection between quantum chemical method development, especially in the 1990s and their application in the course of the investigation of enediyne reactions.

The possibility of using natural enediyne as antitumor antibiotics also triggered calculational studies especially in connection with computer-assisted drug design. These investigations were performed at a time when the medicinal work with natural enediyne had already suffered from setbacks due to their toxicity^{8,18} so that after a period of heavy publication activity, editors had a tendency of “banning” enediyne articles from high-ranking journals. However, these setbacks opened up new perspectives rather than a decline of enediyne chemistry. The focus was now on nontoxic synthetic enediyne derived from their natural counterparts, the extension to hetero- and metallo-enediyne, the use of enediyne as polymers or other materials, and the application of Bergman-type reactions to discover new synthetic routes. Apart from this, it had already become a standard to test new quantum chemical methods for their accuracy by applying them to the benzyne biradicals and the cycloaromatization reactions of the enediyne and enyne-allenes. Hence, an enediyne review in the year 2013 is still carried by the fascination accompanying the natural enediyne as powerful anticancer drugs, the synthetic and mechanistic background of the enediyne reactions as well as the role, which enediyne chemistry still plays in quantum chemistry.

Previous reviews have focused on different aspects of enediyne chemistry including theory, thermodynamics and kinetics, vibrational spectroscopy, synthesis, biosynthesis, and pharmaceutical applications.

- **Theory:** The computational and theoretical background of enediyne was discussed by Schreiner and co-workers in 2005.¹⁹ König and co-workers presented the electronic effects on the Bergman cyclization in 2004,²⁰ whereas Gilmore and Alabugin reviewed the enediyne chemistry in view of the Baldwin's rule for ring closure.²¹ Two recently published reviews of Alabugin and co-workers discuss computational and theoretical studies of cycloaromatization reactions up to the year 2013.^{14,22}

- **Thermodynamics and kinetics:** Wenthold provided an overview of all experimental thermochemical properties of benzyne up to 2010.²³ An earlier summary of benzyne chemistry complemented by a historic overview of their discovery and their applications in synthesis was given by Wentrup,²⁴ Recently, Schmitt et al. addressed the kinetics of the reaction bearing his name.²⁵
- **Vibrational spectroscopy:** In 1998, Sander reviewed the vibrational spectroscopy of *m*- and *p*-benzyne.²⁶
- **Photochemistry:** Recently, Alabugin and co-workers reviewed the photochemistry of enediyne.²⁷
- **Synthesis:** The majority of recent reviews on enediyne give an overview over synthetic accomplishments. Joshi and Rawat published a comprehensive summary of the developments in enediyne chemistry.²⁸ Nicolaou and Chen reviewed the influence of enediyne on the development of total synthesis.²⁹ Maretina summarized design strategies of enediyne and enyne-allenes stretching from organic to metallorganic chemistry.³⁰ Guleskaya and Tyaglivy reviewed the use of enediyne in heterocyclic synthesis.³¹
- **Biosynthesis:** Liang highlighted the progress in the understanding of how natural enediyne are synthesized by nature.³² Kar and Basak presented a comprehensive summary on the design of enediyne and related analogues with pH- or photodependent triggering devices.³³
- **Pharmaceutical applications:** Shao reviewed the therapeutic applications of enediyne antitumor antibiotics,³⁴ and Popik summarized the efforts in the field of photoswitchable enediyne antibiotics.³⁵ Salas and co-workers published a summary on enediyne and related compounds produced from marine actinomycetes.³⁶

This review will provide an overview of the past and current impact of enediyne in the field of computational chemistry. Special focus will be on the following topics: (i) the quantum chemical description of biradicals, (ii) the mechanistic studies of the Bergman cyclization and its related reactions, (iii) the computer-assisted design of target-specific enediyne antitumor drug candidates, (iv) enediyne as tools in syntheses, and (v) the role of enediyne in polymer chemistry and materials science.

THE CHEMISTRY OF ENEDIYNES AND RELATED COMPOUNDS

In Figure 1, the prototypical cyclization reactions of enediynes and enyne-allenes are sketched. In addition to the Bergman cyclization, enediynes can also cyclize to a fulvene biradical **3** via a so-called Schreiner–Pascal cyclization first discussed in this connection by Schreiner.^{37,38} Due to the lack of aromaticity and reduced conjugative stabilization of **3** as compared to **2**, this reaction can energetically not compete with the Bergman cyclization.³⁷ However, as shown in a recent experimental and theoretical study, the thermal cyclization can be enforced by steric hindrance at the alkyne termini.³⁸ Enyne-allenes **4** can perform the Myers–Saito^{39,40} cyclization leading to the α -3-didehydrotoluene biradical **5**, whereas the corresponding Schmitt cyclization⁴¹ generates the fulvene biradical **6**. There have been several reviews, which summarize the experimental investigations of these reactions,^{23–25} and therefore only some of the highlights in the research on enediyne reactions are pointed out here, especially those, which turned out to provide reference data for the quantum chemical investigations on enediynes and their rearrangement products.

The Bergman Cyclization

Bergman^{1,2} demonstrated that the reaction of the parent enediyne **1** is endothermic, has a significant barrier, and occurs only at temperatures higher than 155°C. In view of this limitation, the importance of this reaction in nature was not clear in the 1970s. This changed however dramatically in the mid-1980s. The discovery of the naturally occurring enediynes,^{4–6,8,18} which perform a Bergman reaction to transform into biological active biradicals under physiological conditions, e.g., body temperature and a pH value close to 7, triggered a new wave of studies of this unique reaction. There was the expectation that understanding and copying what nature does could lead to new applications in the field of drug development.

In 1994, Roth et al.⁴² determined the energetics of the Bergman cyclization of **1** with the help of kinetic measurements. They obtained a reaction enthalpy $\Delta\Delta H_0^f$ of 8.5 ± 1.0 kcal/mol. The activation enthalpies $\Delta H^\ddagger(1 \rightarrow 2, 470)$ and $\Delta H^\ddagger(2 \rightarrow 1, 470)$ for forward and backward reaction (see Figure 2), measured at 470 K, were 28.5 ± 0.5 and 19.7 ± 0.7 kcal/mol, which converts to values of $\Delta H^\ddagger(1 \rightarrow 2, 298) = 28.7 \pm 0.5$ kcal/mol and $\Delta H^\ddagger(2 \rightarrow 1, 298) = 20.2 \pm 0.7$ kcal/mol (see Figure 2) according to temperature corrections determined by Kraka and

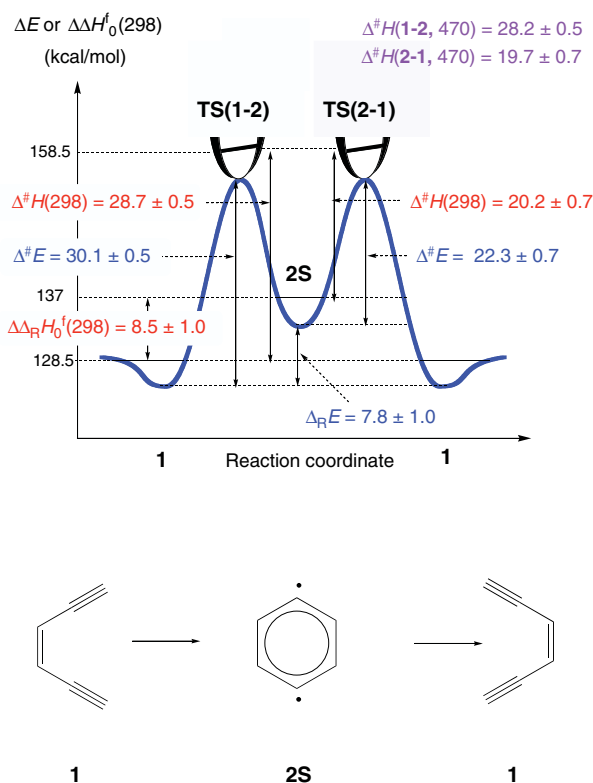


FIGURE 2 | Energetics of the Bergman cyclization of (Z)-hex-3-ene-1,5-diyne **1** as determined by experiment.⁴² The experimental reaction enthalpy $\Delta\Delta H_0^f(298)$, the activation enthalpies for forward and backward reaction, $\Delta H^\ddagger(1 \rightarrow 2, 470)$ and $\Delta H^\ddagger(2 \rightarrow 1, 470)$, respectively, are converted to both enthalpy differences at 298 K and energy differences at 0 K ($\Delta_R E$, $\Delta E^\ddagger(1 \rightarrow 2)$, $\Delta E^\ddagger(2 \rightarrow 1)$) using vibrational corrections calculated at the B3LYP/6-311+G(3df,3pd) level of theory. (Reproduced with permission from Ref 43. Copyright 2000, American Chemical Society.)

co-workers with the help of vibrational frequency calculations.⁴³ The relevant energy values are shown in Figure 2, where the activation enthalpy for the retro-Bergman cyclization is also given because this plays an important role for substituted enediynes as will be shown in the section on natural enediynes and the development of antitumor antibiotics. Noteworthy in this connection is that the energetics of the Bergman cyclization as measured by Roth and co-workers⁴² differed not much from the empirical estimates of Bergman in the early 1970s (32 and 18 kcal/mol for the activation enthalpies; 14 kcal/mol for the reaction enthalpy²).

Energy-resolved collision-induced dissociation (CID) measurements of Wenthold, Squires, and Lineberger (WSL)⁴⁴ determined the heats-of-formation of **2** to be 137.8 ± 2.9 kcal/mol. Combining Roth and co-workers' reaction enthalpy with the heats of formation for **1**, 105.0 kcal/mol,

a heats-of-formation value of 138.0 ± 1.0 kcal/mol for **2** results, which is in convincing agreement with the CID measurements. Biradical **2** was isolated for the first time at low temperature in the matrix and identified by infrared measurements in combination with quantum chemical calculations by the Sander group and Kraka and Cremer.⁴⁵ These authors repeated in this way what they had already accomplished when identifying *m*-benzyne by matrix isolation spectroscopy for the first time.^{46,47} The ground state of biradical **2** was proven to be a singlet in agreement with early predictions of Bergman and in line with what had been found for *m*-benzyne. WSL⁴⁴ reported a singlet-triplet splitting of 3.8 ± 0.4 kcal/mol for **2** where their measurements were based on the photoelectron-spectroscopy of biradical **2** and its anion. A recent comparison of the thermochemical properties of **2** with those of ortho- and meta-benzyne was published by Wenthold.²³

The geometry of the parent enediyne **1** was investigated with the help of microwave spectroscopy by McMahon and co-workers.⁴⁸ The authors obtained an r_0 and r_s -structure from which an r_e geometry was derived with the help of CCSD(T) calculations. The latter geometry is in good agreement with high level *ab initio* calculations and confirms that the alkyne units are slightly bend outward leading to a critical distance C1C6 of 4.32 Å, slightly shorter than most DFT and early CCSD(T) calculations predicted. The CCC angles, indirectly responsible for this distance, turned out to be 123.9° .⁴⁸

In contrast to the Bergman cyclization of **1**, the Myers–Saito cyclization of (*Z*)-1,2,4-heptatriene-6-yne **4** to the α -3-didehydrotoluene biracial **5** occurs at physiological conditions. The estimated activation enthalpy $\Delta H^\ddagger(4 \rightarrow 5)$ is 21.8 ± 0.5 kcal/mol. The reaction is exothermic with a reaction enthalpy $\Delta_R H = -15 \pm 3$ kcal/mol.⁴⁹ Recent multireference-MP2 calculations of Sakai and Nishitani⁵⁰ predict a $\Delta H^\ddagger(4 \rightarrow 5)$ of 16.9 kcal/mol and a $\Delta_R H$ of -14.0 kcal/mol thus confirming the experimental reaction enthalpy, however raising a question about the barrier height. For the Schmittel cyclization of **5**, Sakai and Nishitani⁵⁰ calculated a $\Delta H^\ddagger(4 \rightarrow 6)$ value of 22.9 kcal/mol and a $\Delta_R H = 10.5$ kcal/mol. No experimental data for the Schmittel reaction of **4** has been reported so far.

Controlling the Bergman Cyclization

The naturally occurring enediyne have inspired chemists to make strategical use of the Bergman cyclization in synthesis where these applications ranged from the natural product synthesis of target

enediynes with antibiotic, antitumor activity to the use of designer enediyne in heterocyclic synthesis, polymer chemistry, and materials science.^{21,28,30,31,51} For these purposes, the understanding of the kinetics of the Bergman cyclization and the electronic factors, which determine its barrier and the endothermicity of the reaction, is of fundamental importance. The barrier of the Bergman cyclization is influenced by three dominant factors: (i) the *proximity effect* first introduced by Nicolaou et al.⁵²; (ii) the *molecular-strain differences* first discussed by Magnus et al.⁵³ and Snyder⁵⁴; and (iii) the *electronic effects* influencing the stability of the rearranging enediyne, the corresponding transition state, or the formed biradical.

Proximity Effect

Nicolaou and co-workers^{52,55} derived an empirical rule stating that the critical distance $R(C1C6)$ between the two enediyne carbon atoms forming the new bond (see Figure 3) should be in the range of 3.31–3.20 Å for a spontaneous Bergman cyclization at body temperature (*proximity rule*). This rule has been confirmed and fine-tuned by quantum chemical calculations.^{19,56} Noteworthy in this connection is that at a distance of 3.2 Å the two in-plane enediyne π -orbitals are parallel and resemble the orbital arrangement for the symmetry-forbidden transition state of the [2+2] cycloaddition reaction.⁵⁷ Alabugin and Manoharan point out that at this distance the four-electron repulsive interactions dominate the two-electron bond forming interactions according to a natural bond orbital (NBO) analysis.⁵⁷ At a distance below 3.2 Å, the two-electron stabilization interactions steeply increase thus supporting bond formation.

As Figure 3 reveals, the parent enediyne has a large barrier because of a C1C6 distance of 4.41 Å. This distance can be stepwise reduced by incorporating the enediyne unit into 12- or 10-membered rings where benzoannulation and the incorporation of heteroatoms or sp^2 -hybridized C atoms (double bonds) leads to a further decrease of the critical distance. A spontaneous Bergman reaction is found for benzodecapentaene below 25°C in line with a critical distance of just 3.01 Å.⁵⁸ Figure 3 reveals that not all activation enthalpies follow the proximity rule and that other factors also influence the reactivity of the enediyne.

Nevertheless, the proximity rule helps to understand the reactivity of some natural enediyne, which must be appropriately triggered to become bioactive. For example, dynemicin (see Figure 4) contains in its untriggered form an epoxide that locks the 10-membered enediyne ring in a conformation that

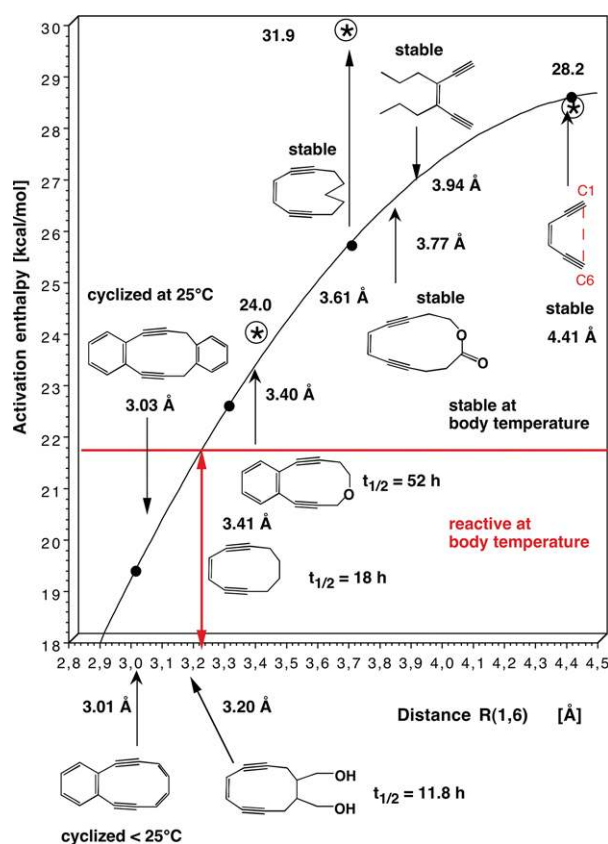


FIGURE 3 | Dependence of the activation enthalpy of the Bergman cyclization of (Z)-hex-3-ene-1,5-diyne on the critical distance between carbon atoms C1 and C6 according to *ab initio* calculations (black dots).⁵⁶ Known C1C6 distances, measured activation enthalpies (starred values), half-life times $t_{1/2}$, and cyclization temperatures are also given.⁵⁵ The deviations of the starred values indicate the limitations of the *ab initio* relationship. (Reproduced with permission from Ref 56. Copyright 1994, American Chemical Society.)

freezes the critical distance at 3.54 Å.⁵⁹ Triggering of dynemicin opens the epoxide ring, changes the conformation of the 10-membered ring, and decreases the critical distance to 3.17 Å. Consequently, the barrier for the Bergman cyclization is lowered from 52 to 17.9 kcal/mol.⁵⁹

Molecular-Strain Differences

Despite a large body of theoretical and experimental evidence supporting the proximity rule, Magnus et al.⁵³ and Snyder⁵⁴ proposed that the driving factor for the Bergman reaction is the difference in strain energies for the ground and transition state of the enediyne. An early study by Magnus and co-workers⁵³ showed that the [7.3.1] bridgehead ketone **7** (see Figure 5) performs the Bergman cyclization already at 70°C whereas the [7.2.1] bridgehead ketone **8**, which possesses a decreased critical distance

of 3.36 Å, reacts about 660 times slower than **7**. The authors explained the unexpected reactivity by pointing out that in **7** the six-membered ring converts from a boat conformation in the starting situation to a chair conformation in the transition state thus reducing its strain energy by about 6 kcal/mol, which lowers its activation energy from 31.2 in **8** to 25.4 kcal/mol in **7**.

In a recent study, Basak and co-workers⁶⁰ compared the cyclization rates of two enediynes with the same critical distance (3.79 Å) but different degrees of saturation in a heterocyclic chromophore linked to the enediyne unit (see **9–12** in Figure 5). Compound **9** contains an aromatic 6 π ring, which forces the heavy atoms of the $-\text{O}-\text{CH}_2$ substituent into the ring plane thus leading to a highly strained eight-membered ring in the transition state **10** of the cyclization. Saturation of the remote double bond in the diaza-cyclohexenone ring of **11** results in a strain relief of the eight-membered ring, which is due to the higher flexibility of the diaza-cyclohexenone unit.

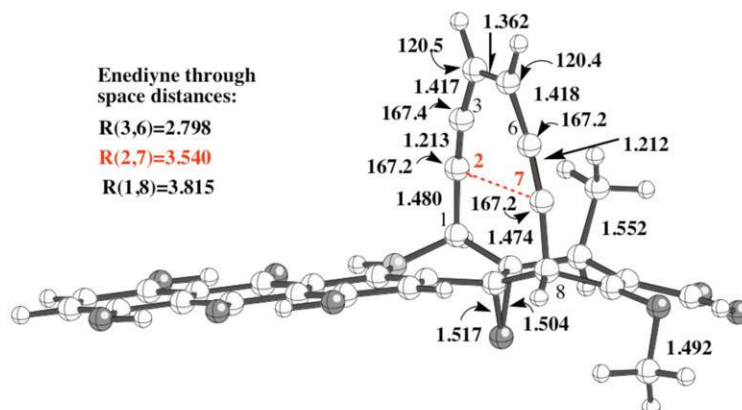
These examples clearly emphasize the general importance of ring strain in the enediyne and related cyclizations. Strain in the starting enediyne will raise its energy, which, with increasing cycloaromatization, will be lowered in the transition state. The proximity rule is a simple measure of this strain, however cannot account for other strain effects resulting from bicyclic structures. Hence, the proximity rule applies only to simple enediyne situations, whereas more complex structures require a detailed strain analysis. All naturally occurring enediynes are incorporated into 9- or 10-membered rings, which increases the strain of the reactant in the sense of the proximity rule. This explains the exclusive focus on the critical distance by those who were involved in the synthesis of natural enediynes.^{61–63}

In a recent review article, Alabugin and co-workers¹⁴ give an appealing analysis of strain effects. They emphasize that strain can act in two different ways, which they discuss for enediynes as follows: Strain induced at the ene unit (incorporation of the double bond in a strained ring) lowers the reactivity of the reactants and accordingly is unproductive, whereas strain induced at the alkyne termini, e.g., by incorporating them in a strained ring, facilitates cycloaromatization and therefore is productive.¹⁴

Electronic Effects

Much effort has been invested into the unraveling of the electronic effects influencing the energetics of the Bergman cyclization.^{19,20,64,65} These effects may be distinguished in the following way: (i) influence of substituents at the terminal alkyne positions,

Dynemicin A, epoxide



Dynemicin A, alcohol

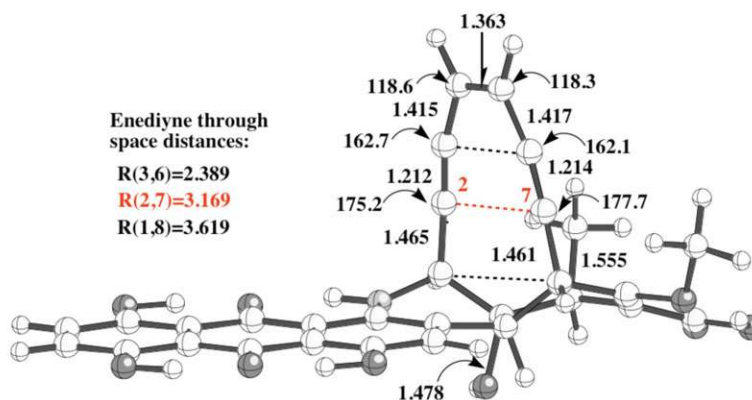


FIGURE 4 | Change in the critical distance C2, C7 (corresponding to C1, C6 in **1**) before and after opening of the epoxide in dynemicin A.⁵⁹

(ii) influence of substituents at the vinyl positions, (iii) benzannulation, and (iv) extension of (iii) to the so-called *ortho-effect* of *o*-positioned benzo-substituents.⁶⁶

(i) *Terminal substitution*. Substituents with σ -withdrawing and π -donating capacity such as $-\text{F}$, $-\text{Cl}$, $-\text{OH}$, NH_3^+ decrease the barrier and endothermicity of the Bergman cyclization whereas σ -donating and π -withdrawing substituents such as $-\text{BH}_2$, $-\text{AlH}_2$ produce the reverse effect.⁶⁵ In the case of substituents with both σ - and π -withdrawing effect such as $-\text{NO}_2$, the σ -withdrawing influence dominates.

In Figure 6(a), the highest occupied π - and σ -orbitals of *p*-benzyne are shown where the nodal planes are indicated by dashed lines. There is another π -orbital close, but lower in energy and with a horizontal nodal plane, which leads to less exchange repulsion between the X orbitals. Also, it has to be mentioned that the C2, C5 coefficients of the π -orbital considered may have positive, negative, or zero value

depending on the electronic nature of X. Normally, the σ -HOMO (highest occupied molecular orbital) is above the π HOMO (actually the HOMO-1); however, this will depend on X.

Substituents with π -donor character will increase the density between atoms C1 and C6 in the π -HOMO, thereby facilitating bond formation between these atoms, which leads to a lowering of the reaction barrier. Substituents with σ -withdrawing character will decrease the electron density in the σ -HOMO, which is C1C6 antibonding (Figure 6(a)). This again will lead to a stabilization of the transition state and, hence, a lowering of the barrier. Even remote substituents at the alkyne terminus can influence the cyclization mechanism, forcing it from a concerted to a stepwise mechanism as was recently shown by Schmittel and co-workers.^{25,67}

(ii) *Vinyl substitution*. It has been found that electron-withdrawing groups such as NO_2 or OH in a vinyl position increase the barrier of the Bergman

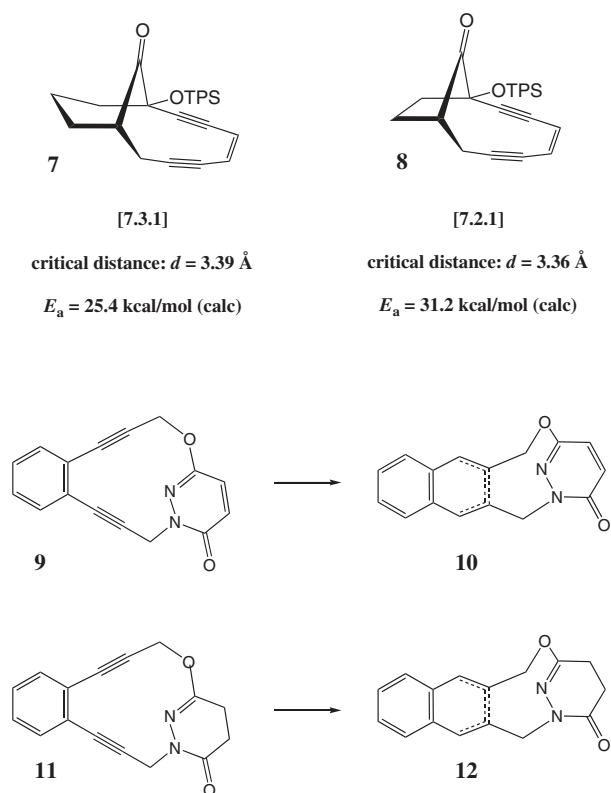


FIGURE 5 | Influence of strain effects on the barrier of the Bergman cyclization.

cyclization. σ -Donating groups lower the barrier, whereas π -donation has only a minor effect.⁶⁴ It was argued that the transition state is “ σ -aromatic” and accordingly stabilized by σ -donating groups; however, no arguments were given why σ -aromaticity is in this case stronger than π -aromaticity.¹⁹ Similarly, one has referred to the nature of the HOMOs shown in Figure 6(a) without providing a consistent explanation of the role of vinyl substituents. An improved discussion of the situation was given by Alabugin and Manoharan.⁶⁸

Special consideration was given to the effect of halogens in vinyl positions, which are known to increase the barrier of the cycloaromatization reaction. Jones and co-workers^{69,70} invoked increasing exchange repulsion between the in-plane Cl electron lone-pair and the in-plane π -electrons, which were assumed to increase in the course of the reaction. No details were given. The situation is sketched in Figure 6(b). Repulsion between the electrons of the orbitals shown will be determined by geometric and hybridization factors. Clearly, the geometric factors are as such that repulsion should decrease rather than increase with the bending at C2. However, the bending involves also a rehybridization of a $p\pi$ - to a

sp^2 -orbital, which extends much more into space and therefore overlaps more strongly with the in-plane lone pair orbital at Cl. It seems that the latter effect dominates, thus causing an increase in the barrier as caused by the Cl substituents.

(iii) *Benzoannulation*. Replacing the enediyne double bond by a benzene ring leads to a special form of vinyl substitution. Under comparable conditions, Roth and co-workers⁷¹ found that for 1,2-diethynylbenzene (see Figure 6(c)) the energetics of the Bergman cyclization significantly changes as is reflected by a 3 kcal/mol decrease in the barrier (decrease from 28.2 kcal/mol in the case of **1** to 25.2 kcal/mol) and a large increase of the endothermicity by 9.4 kcal/mol (from 8.5 to 17.5 kcal/mol). Since benzoannulation reduces the C1C6 distance by more than 0.3 Å, the decrease in the barrier is not unexpected.

The increased endothermicity was attributed to a reduced gain in aromatic stabilization when transforming 1,2-diethynylbenzene to 1,4-didehydronaphthalene **14** compared to the aromaticity gain for the parent enediyne **1**. Benzo-annulation reduces the barrier of the retro-Bergman ring-opening reaction to 7.7 kcal/mol (Figure 6(c)) and makes the hydrogen atom abstraction the rate-determining step. A recent study on aryl-fused quinoxalenediynes⁷² concluded that extending benzoannulation from 1,2-diethynylbenzene in a linear fashion with respect to the enediyne core further increases endothermicity of the Bergman cyclization, whereas extending benzoannulation in an angular orientation (starting with **13** as the parent system) leads to the opposite effects. These trends can be summarized by Clar's rule according to which arenediynes that produce new aromatic sextets lead to more favorable Bergman cyclization products due to increased aromatic stabilization.

(iv) *Ortho-effect* Alabugin and co-workers^{66,73,74} showed that ortho-substitution in benzoannulated enediyne significantly influences the Bergman cyclization via a combination of electronic, steric, and electrostatic effects involving the in-plane orbitals. Electron-acceptor substituents are generally found to accelerate the cyclization because electron repulsion between the occupied in-plane alkyne π -orbitals is reduced in the course of the reaction. However, this can be overruled by steric factors or hydrogen bonding. *Syn*-CHO, *ortho*-NO₂, CF₃, and *syn*-OMe₃ facilitate the Bergman cyclization through steric assistance forcing the alkyne groups to bend. Steric repulsion in the reactant is alleviated in the transition state where the acetylene moiety is bent away from the ortho substituent. CH₃, NH₂, and *syn*-OH increase the activation energy

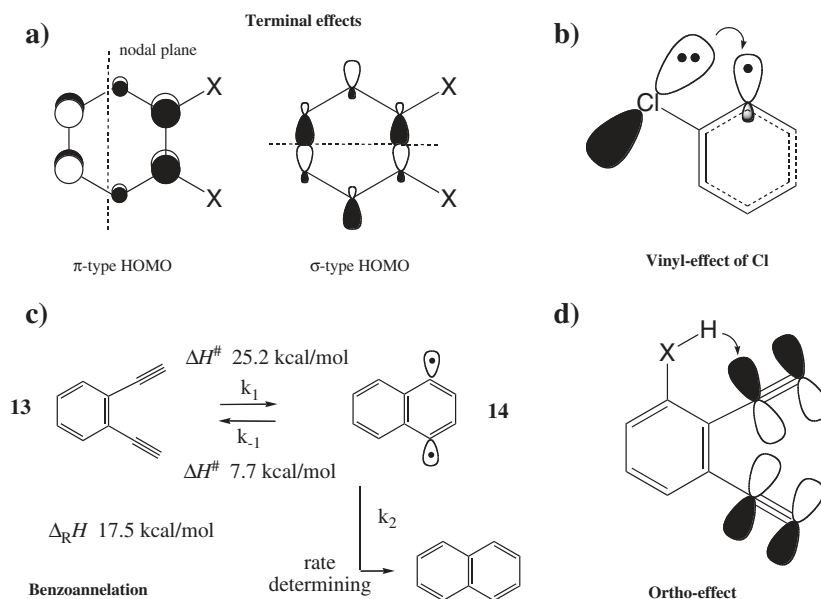


FIGURE 6 | Electronic effects determining the energetics of the Bergman cyclization (see the text).

because they stabilize the starting material by a hydrogen bond between XH and the in-plane alkyne π -orbital (Figure 6(d)). As the reaction proceeds, this stabilizing interaction disappears and is replaced by a H-bond to a radical center. This can lead to an internal H-abstraction reaction and the formation of an oxy radical.

Acyclic Enediyne

New synthetic results in enediyne chemistry have revealed that acyclic enediyne can be thermally stable

and nevertheless undergo the Bergman cyclization at body temperature. In these cases, special electronic effects stabilize the cyclization product, which we will discuss for some examples shown in Figure 7. (For a more comprehensive review, see Ref. 28.)

Lin and co-workers⁷⁵ synthesized acyclic enediyne with aromatic N-heterocycles in the terminal position of the alkyne. Compounds such as **15** and **16** ($X = \text{CH}, \text{N}$) showed growth inhibition effects for $X = \text{N}$ on a full panel of 60 human cancer cell lines. The biradicals of **15** and **16** formed during the Bergman cyclization are stabilized by electrostatic

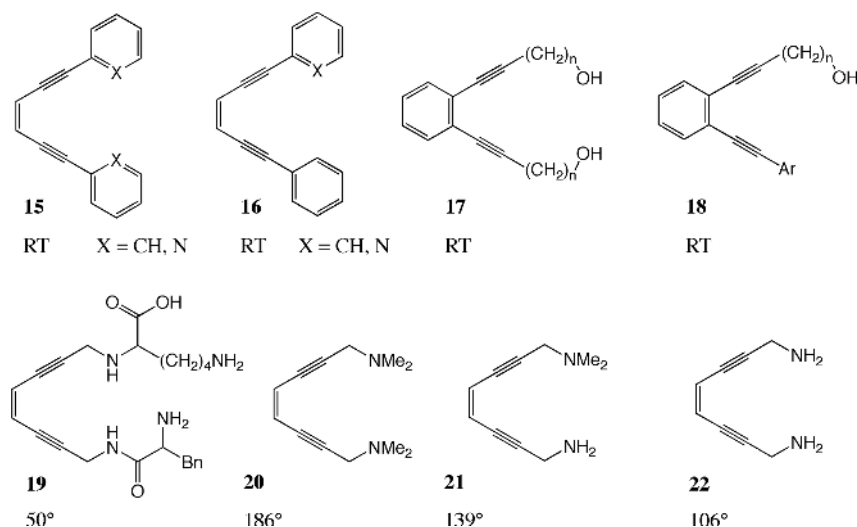


FIGURE 7 | Acyclic enediyne undergoing the Bergman cyclization at either room temperature (RT) or reduced temperature. Temperatures are in $^{\circ}\text{C}$ are given below formulas.

interactions between the two heterocycles, which are free to rotate into a position maximizing intramolecular dipole–dipole attraction. Lo and coworkers⁷⁶ introduced enediynes **17** and **18**, which possess (a) terminal OH group(s) and potent anticancer activity. In these cases, the biradicals are stabilized by hydrogen bonding. Compound **18** displayed a broad spectrum of inhibition for various cancer cell lines. The authors argued that the arene substituent at the terminal alkyne position is needed to obtain antiproliferation.

Jeric and co-workers^{77,78} introduced a general strategy for the preparation of enediyne–amino acid conjugates such as **19**. Their study showed that peptide-based enediynes can undergo Bergman cyclization at relative low temperatures where H-bonding between the terminal groups may play a role. Rawat and Zaleski⁷⁹ investigated the influence of bulky substituents at the alkyne termini of N-substituted enediynes. The barrier for the Bergman cyclization is lowered by 80°C when replacing the bulky NMe_2 substituents in **20** by NH_2 stepwise via **21** to **22** (Figure 7). Compound **22** may turn out to be an important ligand for the synthesis of thermally reactive metallo-enediyne complexes. The Bergman cyclization barriers of diethynyl-imidazole derivatives can be modulated by suitable N-substituents.⁸⁰ In this way, they offer a promising potential for drug design.

COMPUTATIONAL DESCRIPTION OF ENEDIYNES AND THEIR REARRANGEMENT PRODUCTS

The quantum chemical description of enediynes and their reactions is challenged by the fact that in the Bergman, Myers–Saito, or Schmittel reaction always a closed-shell system (the enediyne) rearranges to an open-shell singlet biradical with substantial multireference character. This requires methods, which provide a balanced description of both reactant and product in addition to a cost-effective handling of large molecular systems (Figure 1; R being a bulky group). Because these two requirements were (are) difficult to fulfill, quantum chemists focused in the beginning (i) on the computational investigation of the parent enediyne or enyne-allene system shown in Figure 1 and (ii) on the extensive use of DFT.

DFT Description of Bergman and Related Reactions

Kohn–Sham DFT (KS-DFT) is a single-determinantal method that can in principle describe multireference systems provided the exact exchange–correlation (XC) functional would be known.¹⁷ However, with

the approximate XC functionals nowadays available a restricted DFT (RDFT) description of the Bergman, Schmittel, or Myers–Saito reaction has to fail because of an erroneous description of biradicals **2**, **3**, **5**, and **6** (Figure 1) formed in these reactions. In view of the size of the naturally occurring enediynes, there was (and still is) the dilemma of using a low-cost method such as DFT, but having to describe transition states and products with considerable biradical character. This dilemma motivated the analysis of existing and new DFT methods, which centered around broken-symmetry spin-unrestricted DFT (BS-UDFT),^{43,81} permuted orbital UDFT (PO-UDFT),⁸¹ two-determinant DFT methods such as ROSS (restricted open-shell-singlet)-DFT,⁸² ROKS (restricted open-shell Kohn–Sham) DFT,⁸³ and REKS (restricted ensemble Kohn–Sham) DFT^{84,85} as well as the complete active space DFT (CAS-DFT) method.^{86–88} For each of these methods, the choice of the X and/or C functional turns out to be decisive.

Early success in describing open-shell singlet (OSS) biradicals with UDFT caused many authors to use DFT in situations where this method should fail for principle reasons. This led to a dispute between DFT developers and DFT users where especially enediyne chemistry was the battlefield of contradictory opinions. Scientific disputes tremendously help to clarify methodological questions where in the case of the enediynes the problems concerning the reasonable description of σ , σ - and σ , π -OSS biradicals were solved.

Electron Correlation Effects Relevant in Enediyne-Related Molecules

In Figure 8, four adiabatic connection schemes⁸¹ are given, which schematically describe the electron interaction systems related to enediynes. For $\lambda = 0$, the reference state with noninteracting electrons is defined, which, by increasing λ from 0 to 1, is adiabatically converted into a system with real electron–electron interactions. In the way λ increases, dynamic electron correlation will increase from zero to its full magnitude (correlation energy E_C in Figure 8) and a continuum of intermediate states will connect the reference to the real state of the electronic systems given at the bottom of Figure 8.

As a closed-shell system, an enediyne can be presented in its ground state by one configuration state function (CSF) Ψ_0 , which in turn can be approximated by one Slater determinant Φ_0 , i.e. the ground state of an enediyne can be reasonably described by a single-configurational, single-determinantal wave function. In Figure 8, this is called a type 0 system, which can be satisfactorily described by KS-DFT.

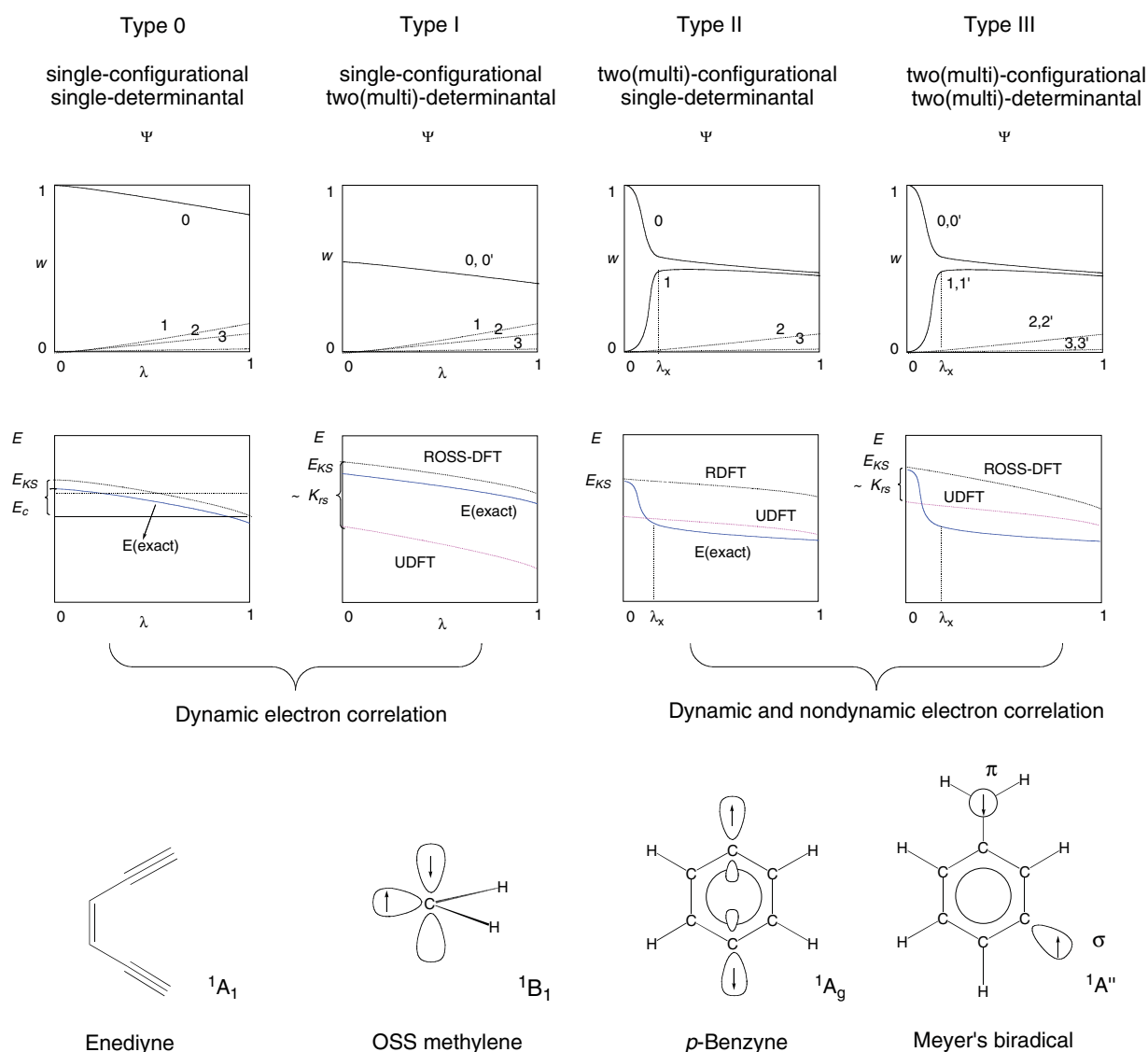


FIGURE 8 | Schematic representation of wave function and energy of type 0, type I, type II, and type III electronic systems as described by RDFT or UDFT with approximate exchange-correlation functionals (dotted lines) or exact Kohn–Sham DFT (solid line).⁸¹ Numbers 0, 1, 2, etc. denote CSF Ψ_0, Ψ_1, Ψ_2 , etc. or determinants Φ_0, Φ_1 , etc. The weights w of the CSF in the true wave function are schematically shown (first row of diagrams) in dependence of the parameter λ that stepwise increases the electron correlation energy E_c from zero ($\lambda = 0$) to its true value ($\lambda = 1$). The corresponding changes in the Kohn–Sham energy E_{KS} and in the exact energy $E(\text{exact})$ (blue) are schematically given in the second row of diagrams. For each type of electronic system, a molecular representative is given at the bottom where one of several electron configurations is indicated. (Reproduced from Ref 81. Copyright 2002, MDPI.)

Excited determinants Φ_1, Φ_2 , etc. (described also as $\Phi_{ijk\dots}^{abc\dots}$, where i, j, k, \dots denote the indices of occupied orbitals, from which electrons have been excited to virtual orbitals a, b, c, \dots) are required in a wave function expansion to describe dynamic electron correlation effects, which are essential for conjugated systems such as the enedynes. This however does not exclude that Φ_0 still dominates the wave function and that these correlation contributions can be assessed by the correlation

functional of DFT leading to the correlation correction E_c .^{81,89}

In the transition state region of the enediyne cyclization reaction, the reactant adopts biradicaloid character. Two different situations emerge depending on whether a Bergman or Schreiner–Pascal reaction (Myers–Saito or Schmittel in case of an enyne-allene) takes place. In the first case, the closed-shell system of the reactant is gradually converted into the open-shell singlet biradical *p*-benzyne that can be essentially

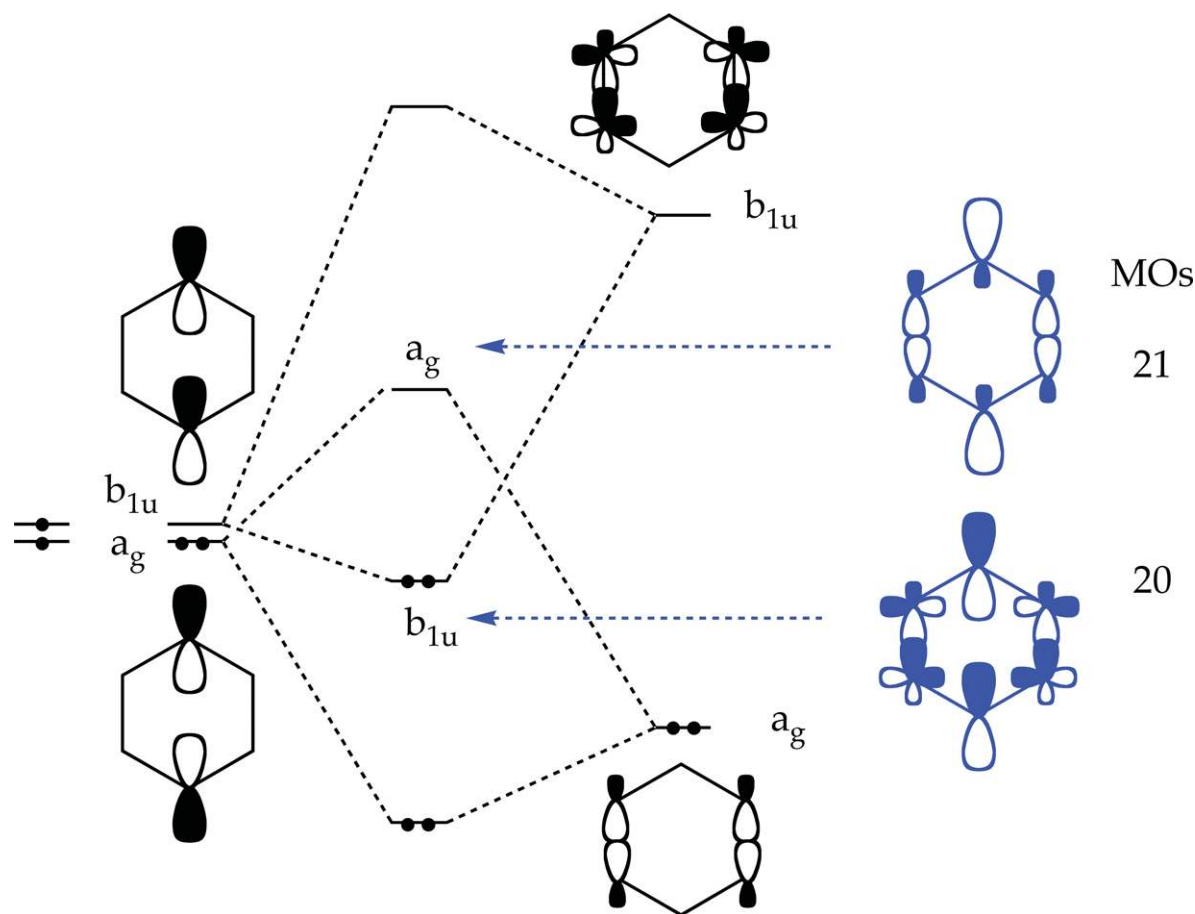


FIGURE 9 | Frontier orbitals of *p*-benzyne (in blue), which result from through-bond interactions involving the singly-occupied orbitals (on the left) and the $\sigma(\text{C2C3}; \text{C5C6})/\sigma^*(\text{C2C3}; \text{C5C6})$ orbitals (on the right).

described by a two-configurational approach in its S_0 ground state where each configuration is given by a single Slater determinant. This corresponds to a type II system in Figure 8. The dominating two Slater determinants for *p*-benzyne are (compare with Figure 9):

$$\Phi_0 : \dots (1b_{3u})^2 (1b_{2g})^2 (1b_{1g})^2 (5b_{1u})^2 (6a_g)^0$$

$$\Phi_1 = \Phi_{ii}^{aa} : \dots (1b_{3u})^2 (1b_{2g})^2 (1b_{1g})^2 (5b_{1u})^0 (6a_g)^2$$

The coefficients of these two Slater determinants reflect the biradical character of *p*-benzyne. The latter successively grows from the transition state to the product where it would be 100% if orbitals $5b_{1u}$ and $6a_g$ would be truly degenerate (see Figure 9). However, the latter can interact with the a_g -symmetrical $\sigma(\text{C2C3}; \text{C4C5})$ and b_{1u} -symmetrical $\sigma^*(\text{C2C3}; \text{C4C5})$ orbitals. This leads to *through-bond electron delocalization* of the single electrons and a lowering of the energies of HOMO and HOMO-1 as shown in Figure 9. The biradical character of

p-benzyne is reduced in the way the molecule is stabilized. However, there is no experiment, which can conclusively determine either the degree of stabilization or the degree of biradical character. This can only be assessed by quantum chemical calculations where simplifications may lead to a bias toward too much or too little biradical character (see below). Again, this will depend on the amount of dynamic electron correlation included by a given method because the latter is also essential to describe through-bond electron delocalization correctly. In any case, *p*-benzyne is a two-configurational, two-determinantal problem (for each configuration only one determinant is needed), which is best described by a multireference method.

As shown for type II systems in Figure 8, the weight w_1 of the determinant Φ_1 strongly increases at some point λ_x so that the wave function is no longer dominated by Φ_0 . The exact energy $E(\text{exact})$ drops at this point substantially below the KS energy thus underlining the importance of nondynamic electron correlation. Dynamic electron correlation effects are

accounted for by small, but significant contributions of excited determinants Φ_2 , Φ_3 , etc.

Multireference Effects Provided by RDFT

RDFT with approximate XC functionals often suffer from the self-interaction error (SIE).⁹⁰ In Hartree–Fock (HF) theory, the self-repulsion energy of an electron is exactly canceled by its self-exchange energy. In DFT, this is no longer the case because of the approximations made when setting up the X functional. Hence, a SIE (X-SIE) results, which can be substantial, especially in the case of odd-electron systems or charge transfer situations.⁹¹ Also, a single electron does not possess any self-correlation energy. C functionals, which are based on wave function descriptions of the correlation hole such as the Lee Yang Parr (LYP) functional (derived from the Colle–Salvetti functional⁹² do not suffer from a SIE (C-SIE); however, this may not be an advantage. Often the X-SIE and C-SIE have opposite signs and therefore cancel each other to some extent where the total SIE is always dominated by the X-SIE.⁸⁹

Cremer and co-workers have investigated the exchange-hole (X-hole) as described by LDA (local density approximation) and GGA (generalized gradient approximation) functionals.^{91–96} These authors showed that the error introduced by the local character of the LDA and GGA X-functionals mimics long-range, left-right correlation effects. This can be made visible by comparing exchange-only DFT electron density distributions directly with coupled cluster density distributions. Both types of densities reveal features that are strongly reminiscent of left-right correlation.⁹⁷

The X-SIE leads to the improved performance of KS-DFT in the case of electronic systems with multireference effects. However, this fact must not be misunderstood as a guarantee that DFT with SIEs can correctly describe multireference systems. The inclusion of nondynamic electron correlation via the SIE of the X-functional is done in a nonspecific way and therefore cannot adjust to the situation of multireference systems with specific nondynamic electron correlation effects. If the SIE-induced correlation effects lead to an improvement of DFT results, it will certainly be for the wrong reason that provides an uncertain starting point for further method (or XC) developments in DFT. Noteworthy in this connection is the fact that hybrid functionals with an increasing portion of exact exchange suffer less from the X-SIE, however become also more unstable in the case of multireference systems. This has to be considered when describing enediyne or enyne-allen reactions with DFT.

An improvement of DFT in the way that multireference effects are explicitly included can lead to a deterioration of results on biradicals such as **2** or **3** compared to the use of XC-functionals with an SIE. This results often from a double counting of correlation effects (specific and nonspecific ones). In such cases, the performance can be improved when replacing GGA functionals such as BLYP with hybrid functionals such as B3LYP because the latter suppress the nonspecific multireference contributions brought about by the X-functional and its SIE. This has often been overlooked in the studies of enediyne reactions.

Broken Symmetry UDFT Description of *p*-Benzyne

Also shown in Figure 8 is the fact that UDFT can mimic the multireference character of type II systems under certain conditions. The UDFT wave function (abbreviated by U) is given as a product of a (closed-shell) core part Ψ_{core} and an open-shell part Ψ_{open} :

$$\Psi^{\text{U}} = \mathcal{A} \left\{ \Psi_{\text{core}}^{\text{U}} \Psi_{\text{open}}^{\text{U}} \right\} \quad (1)$$

(where \mathcal{A} is the antisymmetrizer; $\Psi_{\text{core}}^{\text{U}}$ will no longer represent an exact closed-shell function in the final unrestricted wave function due to the independent optimization of the α - and β -spin orbitals). In the case of *p*-benzyne, $\Psi_{\text{open}}^{\text{U}}$ is constructed from the b_{1u} -symmetrical HOMO and the a_g -symmetrical lowest unoccupied molecular orbital (LUMO) for the purpose of yielding a broken-symmetry UDFT (BS-UDFT) description of the 1A_g state (Figure 8). This is achieved by mixing the HOMO and the LUMO of the closed shell RDFT description of the 1A_g state.^{43,81}

$$\Psi_{\text{open}}^{\text{BS-U}} = |\psi_r \bar{\psi}_s\rangle \quad (2)$$

where the bar denotes a β spin orbital, and the spin orbitals are given by

$$\begin{aligned} \psi_r &= \cos \theta \psi_{\text{HO}} + \sin \theta \psi_{\text{LU}} \\ \psi_s &= -\sin \theta \psi_{\text{HO}} + \cos \theta \psi_{\text{LU}} \end{aligned} \quad (3)$$

The orbital rotation angle θ is optimized during the self-consistent field (SCF) iterations. The resulting orbitals ψ_r and ψ_s are the localized counterparts of HOMO and LUMO, respectively (see Figure 10). Using Eq. (2), the open-shell part $\Psi_{\text{open}}^{\text{BS-U}}$ of the BS-UDFT wave function can be written in the form of Eq. (4).

$$\begin{aligned} \Psi_{\text{open}}^{\text{BS-U}} &= \cos^2 \theta |\psi_{\text{HO}} \bar{\psi}_{\text{HO}}\rangle - \sin^2 \theta |\psi_{\text{LU}} \bar{\psi}_{\text{LU}}\rangle \\ &+ \sqrt{2} \cos \theta \sin \theta |\psi_{\text{HO}} \bar{\psi}_{\text{LU}}\rangle^T. \end{aligned} \quad (4)$$

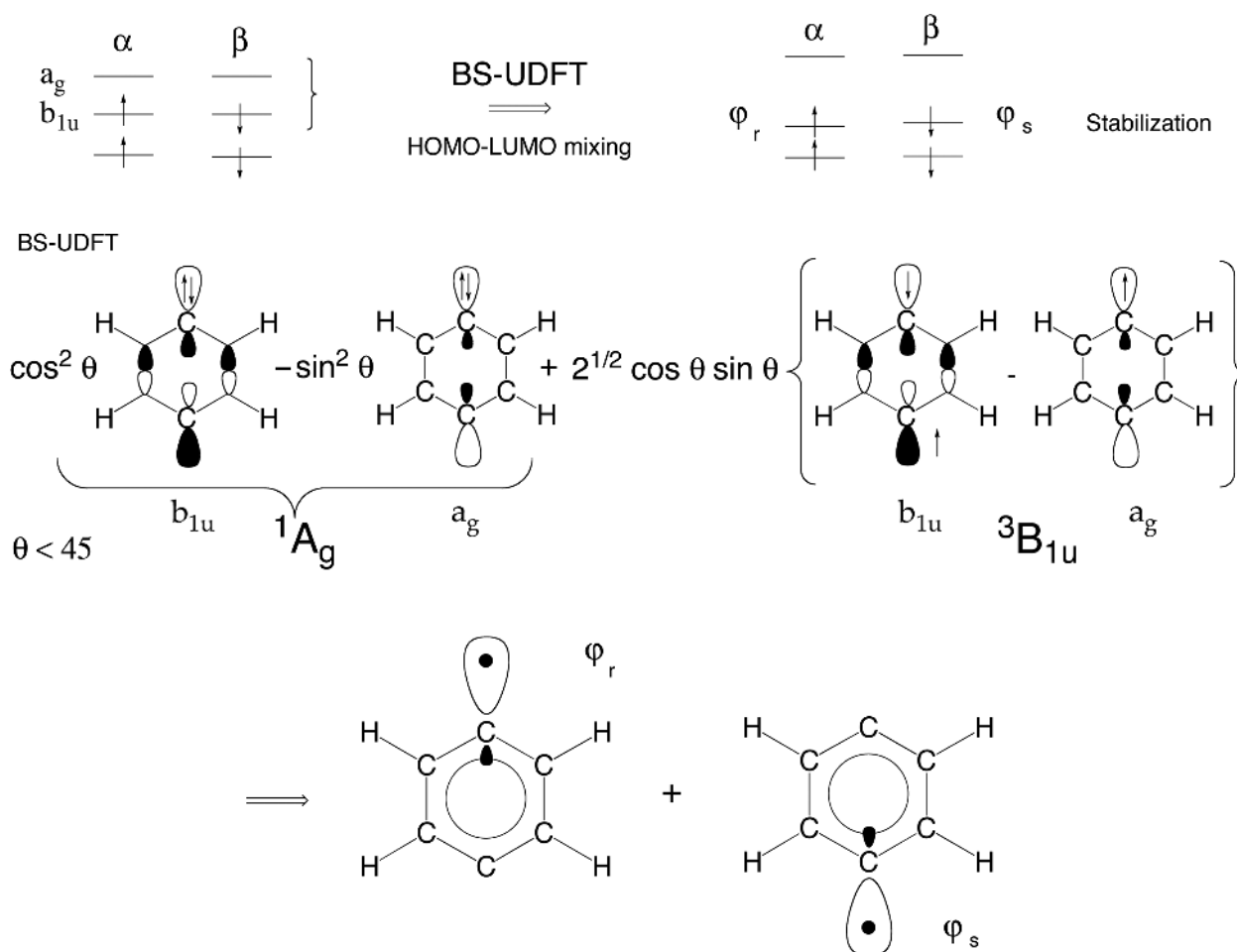


FIGURE 10 | Schematic representation of the 1A_g state of *p*-benzyne by a BS-UDFT wave function. The HOMO–LUMO mixing is given schematically where the form of the frontier orbitals has been simplified to local orbitals ϕ_r and ϕ_s .

where HO and LU denote the HOMO and LUMO. A bar over the orbital symbol indicates β -spin, and the triplet function is given by

$$|\psi_{b_{1u}} \overline{\psi_{a_g}}\rangle^T = \frac{1}{\sqrt{2}} (|\psi_{b_{1u}} \overline{\psi_{a_g}}\rangle - |\psi_{a_g} \overline{\psi_{b_{1u}}}\rangle). \quad (5)$$

Hence, the BS-UDFT state is a mixture of the $|\psi_{HO} \overline{\psi_{HO}}\rangle$ and $|\psi_{LU} \overline{\psi_{LU}}\rangle$ singlet states and the $|\psi_{HO} \overline{\psi_{LU}}\rangle^T$ ($M_S = 0$) triplet state. The spin symmetry is broken, and with respect to the spatial symmetry, the BS-UDFT reference state does not belong to any irreducible representation but is part of a reducible representation that consists of a 1A_g and a $^3B_{1u}$ contribution for *p*-benzyne. However, the BS-UDFT reference function is not completely asymmetric: It belongs to an irreducible representation of a mixed spin-space symmetry group where all reflections at the mirror plane are combined with a simultaneous flip of all spins in the system.⁸¹

The BS-UDFT wave function has two-configurational character similar to that of the generalized valence bond approach for one electron pair (GVB(1)).⁹⁸ Hence, the BS-UDFT orbitals ψ_r and ψ_s resemble the corresponding GVB orbitals (see Figure 10). However, the BS-UDFT wave function does not adopt the two-configurational (two-determinantal) form given by the first two terms in Eq. (4) (ground state and doubly excited state) because the admixture of the triplet state function leads to a collapse of the wave function to a single determinantal form. The amount of nondynamic electron correlation accounted for by a BS-UDFT description can be directly assessed from the rotational angle θ driving the mixing of HOMO and LUMO. Since for a given problem, it may be difficult to determine the optimized θ value and the exact form of Eq. (4), it is easier to calculate the natural orbitals of the BS-UDFT wave function.^{81,99} The fractional values

TABLE 1 | Energetics of the Bergman Cyclization of **1**

Method/Basis Set	$\Delta E^\ddagger(1-2)$		$\Delta E^\ddagger(2-1)$		$\Delta_R E$		T-S		Ref.
	Sum ^d		Sum ^d		Sum ^d		Sum ^d		
SVWN/cc-pVTZ	19.2	17.1	18.6	18.6	6.8	8.8	0.6	−1.5	43
BP86/cc-pVTZ	24.6	21.9	18.6	18.6	4.0	6.7	6.0	3.3	43
BPW91/cc-pVTZ	25.4	22.8	20.0	20.0	3.6	6.3	5.4	2.8	43
BLYP/cc-pVTZ	28.6	25.8	15.1	15.1	4.5	7.3	13.6	10.8	43
B3PW91/cc-pVTZ	31.2	29.0	28.5	28.5	2.4	4.6	2.7	0.5	43
B3LYP/6-31G(d,p)	31.2	28.9	27.9	27.9	2.5	4.7	3.3	1.1	43
B3LYP/cc-pVTZ	34.4	32.1	24.3	24.3	2.6	4.9	10.1	7.8	43
B3LYP1/6-31++g(3df,3pd)	34.1	31.8	24.0	24.0	2.6	4.9	10.1	7.8	43
CCSD(T)/6-31G(d,p)	29.5		24.0		5.5		2.5		56,98
Experimental ^b	30.1 ± 0.5		22.2 ± 0.7		7.8 ± 1.0		3.5 ± 0.5		42,44

Method/Basis Set	$\Delta H^\ddagger(1-2)$		$\Delta H^\ddagger(2-1)$		$\Delta_R H$		T-S		Ref.
CCSD(T)/cc-pVDZ	27.1		23.0		4.1				19
CCSD(T)/cc-pVTZ	27.9		19.4		8.5				100
BD(T)/cc-pVTZ	28.9		18.6		10.3		3.4		19
CASSCF/ANO	43.6		15.9		27.7		3.0		101
GVB-PT2/6-31G(d)	34.8		35.5		−0.7				102
CAS(12,12)PT2/ANO	23.9		20.1		3.8				103
CAS(10,10)PT2/ANO-L	25.2		15.7		9.5				104
CAS(12,12)PT2/ANO-L	25.0		16.4		8.6				104
MRCI/cc-pVTZ	29.4		19.1		10.3				100
MRBWCSD/cc-pVTZ	32.7		19.9		12.9				100
Experimental	28.7 ± 0.5		20.2 ± 0.7		8.5 ± 1.0		3.8 ± 0.5		42,44

^a Sum formula according to Eq. (7) used.^b Experimental enthalpies corrected to energies at 0 K.

of the natural orbital occupation numbers of the mixing orbitals provide then a simple measure of the amount of nondynamic electron correlation covered by the BS-UDFT wave function.⁸¹ This depends however on the XC functional used.

In Table 1, some selective BS-UDFT results are compared with the experimental values of Roth and co-workers,⁴² which have been corrected to energies at 0 K without zero-point energy using calculated vibrational frequencies.⁴³ The stationary points of the Bergman reaction were first calculated with RDFT, then each RDFT solution was tested with regard to its internal and external stability.^{105,106} The singlet state of the biradical turned out to be externally unstable thus indicating a breaking of the constraint $\psi_\alpha = \psi_\beta$. The eigenvector associated with the negative eigenvalue of the stability matrix leads outside the restricted subspace thus yielding a UDFT energy lower than the RDFT energy.

The reliability of the BS-UDFT description of the S state of biradical **2** can be improved by applying the sum rule.^{107,108} The sum formula is based on the assumption that (i) the expectation value $\langle \hat{S}^2 \rangle$ can be calculated from KS orbitals and (ii) the predominant

contamination of the S state results from a low-lying T state. Then, the BS-UDFT energy of **2S** can be corrected according to Eqs. (6) and (7).

$$E(\text{UDFT}, 2\text{S}) = x E(2\text{S}) + (1 - x) E(2\text{T}) \quad (6)$$

$$E(2\text{S}) = \frac{1}{x} E(\text{BSUDFT}, 2\text{S}) - \frac{(1 - x)}{x} E(2\text{T}) \quad (7)$$

where x is determined with Eqs. (8) and (9):

$$\langle \hat{S}^2 \rangle_{\text{BSUDFT}, 2\text{S}} = x \langle \hat{S}^2 \rangle_{2\text{S}} + (1 - x) \langle \hat{S}^2 \rangle_{2\text{T}} \quad (8)$$

$$x = \frac{\langle \hat{S}^2 \rangle_{\text{BSUDFT}, 2\text{S}} - \langle \hat{S}^2 \rangle_{2\text{T}}}{\langle \hat{S}^2 \rangle_{2\text{S}} - \langle \hat{S}^2 \rangle_{2\text{T}}} \quad (9)$$

As can be seen from Table 1, the sum formula improves results, especially by reducing the S-T splitting, which comes out too large at the BS-UDFT level. In general, results obtained with a hybrid functional are closer to experiment on the average than those obtained with a GGA functional. This is due to the fact that the SIE error of the latter and the implicit two-configurational character of the BS-UDFT solution lead to a double-counting of correlation

errors.⁸⁹ The DFT work on the Bergman cyclization suggests that the performance of BS-UDFT has to be evaluated by referring to the total and on-top pair density distributions rather than the KS orbitals and the spin density distribution because the former do not suffer from the symmetry-breaking problem.⁴³

The description of the Schreiner–Pascal biradical 3 (Figure 1), which is essentially a 1,4-butadienyl biradical stabilized by through-bond interactions involving the bonding and antibonding $\sigma(\text{C4C5})$ orbitals, is more challenging than that of *p*-benzyl 2 because of the branching points in the conjugated system and the lower symmetry. Nevertheless, BS-UDFT with an appropriate XC functional can also provide in this case reasonable results.¹⁹

Permuted Orbital UDFT Description of the Meyers–Saito Biradical

The situation is however different in the case of the $\sigma-\pi$ -radicals 5 and 6. A BS-UDFT description is not useful, which can be explained by considering the σ, π -OSS 1B_1 state of methylene as a prototype for such a biradical. In the 1B_1 OSS state of methylene, the electron with α - (β -)spin can occupy either the σ (π) or the π (σ) orbital and both possibilities have to be included into the wave function thus leading to a two-determinantal CSF without any nondynamic electron correlation; there is just dynamic electron correlation (type I system in Figure 8). KS-DFT as a single-determinant method cannot describe the two-determinantal wave function. There is however a possibility of handling such a problem in form of a PO-UDFT calculation.^{81,99}

When constructing the PO-UDFT wave function, the order of the orbitals is changed for one of the spin orientations, for example, by exchanging HOMO and LUMO for the β spin orientation. This leads for the open-shell part of the OSS state of methylene according to Eq. (10):

$$\Psi_{\text{open}}^{\text{PO-U}} = |\psi_{\sigma}\overline{\psi_{\pi}}\rangle \quad (10)$$

The resulting initial state is a mixture of a $\sigma\pi$ singlet and a $\sigma\pi$ triplet component with equal weights:

$$|\psi_{\sigma}\overline{\psi_{\pi}}\rangle = \frac{1}{\sqrt{2}} (|\psi_{\sigma}\overline{\psi_{\pi}}\rangle^T + |\psi_{\sigma}\overline{\psi_{\pi}}\rangle^S) \quad (11)$$

$$|\psi_{\sigma}\overline{\psi_{\pi}}\rangle^S = \frac{1}{\sqrt{2}} (|\psi_{\sigma}\overline{\psi_{\pi}}\rangle + |\psi_{\pi}\overline{\psi_{\sigma}}\rangle) \quad (12)$$

$$|\psi_{\sigma}\overline{\psi_{\pi}}\rangle^T = \frac{1}{\sqrt{2}} (|\psi_{\sigma}\overline{\psi_{\pi}}\rangle - |\psi_{\pi}\overline{\psi_{\sigma}}\rangle) \quad (13)$$

The correct two-determinantal wave function of the OSS state is contained in the PO-UDFT wave

function so that the 1B_1 state of methylene can be adequately described. However, the price for recovering the singlet state within the single-determinantal PO-UDFT wave function is a contamination by the two-determinantal triplet component with $M_S = 0$. Superposition of singlet and triplet components breaks the spin symmetry of the closed-shell initial state. With regard to the spatial symmetry, the PO-UDFT reference state will belong to a one-dimensional irreducible representation ($^{1,3}B_1$), which is antisymmetric with respect to the symmetry plane containing the molecule.

The σ, π -biradical 5 and 6 of the Myers–Saito or Schmittel reaction are type III rather than type I systems. This results from a mutual spin-polarization of the two unpaired electrons. Type III systems (Figure 8) require a two-determinantal, two-configurational description, i.e. the wave function can only be represented by two (or more) CSFs Ψ_0, Ψ_1 , etc., each of which must be spanned by two (or more) Slater determinants Φ_i, Φ'_i , etc. The Meyers biradical (α -3-didehydrotoluene, Figure 8) possesses a singlet ground state because of spin polarization effects between the unpaired electrons. Both normal RDFT, UDFT, BS-UDFT, or PO-UDFT fail in such a situation. Possible are only DFT methods, which explicitly include multireference effects.

Description of Biradicals with ROSS, REKS, and CAS-DFT

ROSS is limited to the application of σ, π -biradicals. The method yields for biradical 5 a reasonable geometry, however fails to predict the singlet to be more stable than the triplet, which indicates that spin-polarization is not correctly described. REKS is limited to a (2,2) active space, which excludes a reasonable account of the energetics of the Bergman or Meyers–Saito reaction. However, Cremer and co-workers used REKS(2,2) to calculate the singlet–triplet splitting of biradical 2.^{81,99} A value of 2.5 kcal/mol (see Table 2) was obtained provided a hybrid functional such as B3LYP was used. The method leads to much larger values with pure XC functionals reminiscent of a double counting of correlation effects in the case of the singlet.^{81,99} The most promising results have been obtained with CAS(8,8)DFT (for singlet–triplet splittings) and CAS(12,12)DFT (for the energetics of the Bergman reaction).^{86–88} In the latter case, however results clearly suffer somewhat from the shortcomings of the CASSCF approach, which cannot be offset by the DFT correlation functional. It is of course of advantage that CAS-DFT can describe reasonably

TABLE 2 | Energetics of the Myers–Saito and Schmittel Cyclization of **4**

Method/Basis Set	$\Delta H^\ddagger(4-5)$	$\Delta H^\ddagger(5-4)$	$\Delta_R H$	T-S	Ref.
UBS-B3LYP/6-31G(d,p) ^a	24.0	37.6	−13.6		19
REKS-BLYP/6-31G(d)	20.0	28.3	−8.3		109
PO-UDFT-B3LYP/6-31G(d)				−1.0	81
CAS(8,8)-DFT/6-31G(d)				−2.5	81
UHF-CCSD(T)/6-31G(d,p)	22.3	34.7	−12.4		110
UHF-BD(T)/6-31G(d,p)	22.3	36.4	−14.1		110
CASSCF(10,10)/6-31G(d,p) ^b	31.1	34.2	−3.1		50
MRMP2/6-31G(d,p) ^b	17.4	32.4	−15.0		50
MRMP2/6-311+G(d,p) ^b	16.9	30.9	−14.0		50
MR-CI+Q/6-31G(d) ^c	27.9	44.0	−17.0		111
Experimental	21.8 ± 0.5	36.8 ± 2.5	−15 ± 3	−5	112

Method/Basis Set	$\Delta H^\ddagger(4-6)$	$\Delta H^\ddagger(6-4)$	$\Delta_R H$	T-S	Ref.
UBS-B3LYP/6-31G(d,p) ^a	31.4	42.3	10.9		19
REKS-BLYP/6-31G(d)	33.4	49.9	16.5	3.2	109
CASSCF(10,10)/6-31G(d,p) ^b	39.1	61.2	22.1		50
MRMP2/6-31G(d,p) ^b	42.0	34.9	10.9		50
MRMP2/6-311+G(d,p) ^b	22.9	33.4	10.5		50
MR-CI+Q/6-31G(d) ^c	35.0	47.0	12.0	5.0	111

^a Free energy differences are given.^b Energy differences including ZPE (zero-point energy) corrections are given.^c Energy differences are given.

any of the three biradical formation reactions, which is not true for either BS-UDFT, REKS, or ROSS.

Single Reference Coupled Cluster Theory

Correlation-corrected wave function methods usually start from the HF mean-field orbitals. Hence the shortcomings of the HF orbitals have to be gradually corrected at the correlated level by the single (S) excitations and their coupling to other excitations effects. This will be effective if the infinite order effects of CC theory are included, and these are coupled to the important double (D) excitations describing pair correlation effects so that in the space of the S and D excitations a full configuration interaction (FCI) quality is achieved within a CCSD calculation.¹¹³ If a CCSD (CC with all S and D excitations) approach is augmented by perturbative triple (T) excitations (CCSD(T)),¹⁵ there are terms in the CC expansion, which account for the multireference character of type II systems (see Figure 8).^{114,115} For example, a disconnected quadruple (Q) term can describe the pair correlation for the doubly excited configuration Φ_1 of *p*-benzyne. Also, the three-electron effects accounted for by the T excitations can describe through-bond delocalization effects of the *p*-benzyne biradical appropriately so that a balance between biradical and closed-shell character can be provided.¹¹⁵

There is however a significant difference whether to perform the CC calculation of the *p*-benzyne with a spin-restricted or a spin-unrestricted CC ansatz. For example, spin-restricted CCSD(T) (RCCSD(T)) provides reasonable energies and geometries for the Bergman cyclization of the parent enediyne **1**, as was first demonstrated by Kraka and Cremer.^{56,98} However, it fails to describe second-order and higher order response properties of *p*-benzyne such as harmonic vibrational frequencies or infrared intensities.¹¹⁶ This is a result of orbital instability effects caused by the existence of low-lying excited states, which can mix with the ground state in the sense of a pseudo-Jahn–Teller effect (PJTE).¹¹⁷ A second-order expression for describing the energy effects of this orbital instability can be obtained by a Taylor expansion of the molecular energy at the equilibrium geometry for a given normal mode coordinate Q_μ as it is done in the case of the PJTE¹¹⁷:

$$E_\mu(2) = \frac{1}{2} \left\langle \Phi_0 \left| \frac{\partial^2 H}{\partial Q_\mu^2} \right| \Phi_0 \right\rangle Q_\mu^2 + \sum_k \frac{\left| \left\langle \Phi_0 \left| \frac{\partial H}{\partial Q_\mu} \right| \Phi_k \right\rangle \right|^2}{E_0 - E_k} Q_\mu^2 \quad (14)$$

where Φ_0 and Φ_k represent the 1A_g ground state of 2 and a perturbing state k , respectively. The first term in Eq. (14) involves the diagonal contribution to the quadratic force constant in the absence of the state interaction, and the second term the magnitude of these interactions where $\langle \Phi_0 | \partial H / \partial Q_\mu | \Phi_k \rangle$ denotes the vibronic coupling element between ground state and excited state k . The second term will be nonzero only if the direct product of the irreducible representations of Q_μ , Φ_0 , and Φ_k contain the totally symmetric representation of the molecular point group. If the perturbing state, Φ_k , lies higher in energy than Φ_0 , then the second term in Eq. (14) will be negative and, depending on its magnitude, may cause an energy lowering upon distortion of the molecular geometry along the symmetry-breaking normal mode Q_μ . If either states 0 and k are close in energy thus yielding a small denominator in the second term or the nonadiabatic coupling matrix element in the numerator is significant, the PJTE will be substantial and affect the second order response properties of *p*-benzyne.

It has been shown¹¹⁶ that the excited $^1B_{1u}$, $^1B_{2g}$, or $^1B_{1g}$ states of *p*-benzyne generated by an electron excitation from the HOMO (b_{1u}), HOMO-1 (b_{2g}), or HOMO-2 (b_{1g}) to the LUMO (a_g) cause a PJTE in combination with normal modes of exactly these symmetries. A measure of the importance of the PJTE is provided by the eigenvalues of the molecular orbital Hessian et al.,¹¹⁸ i.e. the second derivative of the HF energy with respect to orbital rotations, whose inverse implicitly appears in the second term of Eq. (14). Although none of these eigenvalues was found to be negative, their near-zero magnitudes lead to nonsensical vibrational frequencies and infrared intensities for the three modes with b_{1u} , b_{2g} , and b_{1g} symmetry even for the highly correlated RCCSD(T) wave function. In the case of less correlated approaches such as Møller–Plesset perturbation theory^{119,120} at lower order, the deficiencies of the restricted Hartree-Fock starting orbitals cause imaginary harmonic vibrational frequencies. In this connection, it has to be noted that deficiencies of a given correlated method in overcoming the multireference or orbital instability errors when describing the biradicals generated in the course of the cyclization of an enediyne or enyne-allene cannot be compensated by the use of larger basis sets.¹¹⁶

The orbital instabilities in the case of *p*-benzyne can be avoided by using either spin-restricted Brueckner orbitals and the BD(T) (Brueckner doubles and perturbative triple excitations) method.^{121,122} Brueckner orbitals are obtained by rotating the orbitals in such a way that the S excitations of the CCSD expansion are eliminated, which obviously alleviates the deficiencies of the spin-restricted

HF mean-field orbitals. This approach has also been used for describing the σ, π -biradicals of the Myers–Saito and Schmittel reaction after mixing the a' -symmetrical HOMO with the a'' -symmetrical LUMO and obtaining in this way better suited delocalized MOs for the BD(T) calculation.^{19,123}

Alternatively, one can revert to a spin-unrestricted HF (UHF) description to obtain better suited reference orbitals for the CC calculations, which no longer lead to the orbital instability effects of the spin-restricted orbitals.¹¹⁶ The problem of spin contamination is not pendant because the triplet contaminants are completely annihilated by the infinite-order (or FCI) effects in the S- and D-excitation space of CCSD and any higher CC method. However, it was also shown¹¹⁶ that correlation-corrected UHF methods that do not include infinite order effects in the SD-space cannot provide reliable results for *p*-benzyne because of the unusually large spin contamination resulting from two rather than just one triplet state.

The first experimental evidence for the generation of a *p*-benzyne resulted from matrix-isolation spectroscopy⁴⁵ where the positive identification of the biradical could only be accomplished by calculating its infrared spectrum (then done utilizing BS-UB3LYP). A RCCSD(T) description, despite the many times larger computational effort, would not have been suitable in this case because of the orbital instabilities of the starting HF wave function. However, an UHF-CCSD(T) description of the IR spectrum fully confirmed the original BS-UB3LYP description. Similar considerations as discussed here for *p*-benzyne also apply to other biradicals such as *m*-benzyne.^{46,47,124}

In Table 1, CCSD(T) and BD(T) activation and reaction enthalpies $\Delta H^\ddagger(298)$ and $\Delta_R H(298)$, respectively, for the Bergman cyclization are listed. The CCSD(T)/cc-pVTZ enthalpies¹⁰⁰ deviate by less than a kcal/mol from experiment, whereas the BD(T)/cc-pVDZ enthalpies¹⁹ deviate by maximally 2 kcal/mol, which could result from the use of a BS-UBPW91/cc-pVDZ geometry.

Multireference Descriptions

The first complete active space SCF (CASSCF) calculation by Koga and Morokuma used a (10,10) active space (10 electrons in 10 orbitals) with a basis set of moderate size.¹²⁵ CASSCF¹²⁶ carries out a FCI calculation for the active space and also optimizes the orbitals. Although it should provide the correct multireference character of σ , σ^- or σ, π -biradicals or -biradicaloids, it does not guarantee a reliable account of the energetics of an enediyne or enyne-allene cyclization reaction. First of all, the definition of the active space is a nontrivial problem. Koga and

Morokuma included the six out-of-plane and the four in-plane π -electrons of the reactant.¹²⁵ This however leads to an unbalanced active space for the product because in this case through bond delocalization is described for just one half of the molecule. For a balanced description, the other pair of σ -electrons (contributing to the ene-double bond) has to be included thus leading to a (12,12)-active space. Of course, one could also consider whether geminal interactions between σ -bonds must be included, which would lead to a (20,20)-active space, which is beyond what is possible in a CASSCF calculation today.

CASSCF calculations also fail to describe the Bergman (see Table 1) or any other of the related rearrangement reactions correctly because CASSCF (or multiconfigurational SCF, MCSCF) as well as HF lack the important dynamic electron correlation effects. Therefore, they have to be combined with a dynamic electron correlation method such as configuration interaction (CI) or perturbation theory.

Multireference Descriptions of the Bergman and Related Reactions Including Dynamic Electron Correlation

There are only a few multireference investigations with dynamic electron correlation included, which have investigated both the energetics of the Bergman cyclization and the singlet–triplet splitting of the *p*-benzyne. CASPT2(8,8) (CASSCF with second-order perturbation theory for a eight electron, eight orbital active space) and CASPT2 (10,10) calculations suffer from the shortcomings of an unbalanced active space (see above).^{101,104}

The minimum requirement for the active space is fulfilled by CASPT2(12,12) calculations.^{103,104} At the CASPT2(12,12)/ANO (atomic natural orbital basis set) level of theory, Lindh and co-workers obtained an activation enthalpy ΔH^\ddagger (298) that is too low by 3 kcal/mol whereas the endothermicity of the reaction was correctly described (see Table 1). This suggests that the stability of the enediyne is underestimated. Most likely, this is a result of an insufficient account of dynamic electron correlation needed for the appropriate description of electron delocalization in the enediyne. In the course of the Bergman cyclization, the number of electron pairs is reduced by one, which leads also to a significant change in the dynamic two- and three-electron correlation effects. Whereas the former are accounted for by CASPT2, the latter are not.

Recently, Sakai and Nishitani⁵⁰ carried out a multireference second-order perturbation theory (MRMP2) study of the Myers–Saito reaction using

an (10,10) active space and CASSCF(10,10) geometries. They found a C_1 -symmetrical transition state (activation energy 16.6 kcal/mol) and a C_s -symmetrical transition state (18.1 kcal/mol) where the first related to the Myers–Saito biradical 5 (reaction energy –16.2 kcal/mol) and the second to 5 with the methylene group standing perpendicular the benzene ring, i.e. to the transition state of methylene rotation. Clearly, the second path via the C_s -symmetrical transition state must bifurcate (caused by rotation of the methylene group) to reach the final product 5. Although two transition states involving different π -orbitals to form the new C1C6 bond can exist, there is need to confirm these results by a better way of determining the transition state geometries (including also dynamic electron correlation effects). Noteworthy is that the authors⁵⁰ also determined different transition states for the Schmittel reaction.

In connection with the MRMP2 results for the Myers–Saito reaction, it has to be mentioned that Carpenter did extensive CASPT2 studies for the same reaction, which he summarized in a 2006 review on nonadiabatic thermal reactions of organic molecules.¹²⁷ In this review, he points out that the cycloaromatization of enyne-allene 4 in methanol as a solvent leads to 2-phenylethanol and benzyl methyl ether in a ratio of 1:3. The former product can be expected as a result of H-abstraction from the methyl group of the solvent. According to Carpenter, the latter speaks for the formation of a thermally excited zwitterionic state. However, all attempts to describe such a state by CASPT2 calculations¹²⁷ led to excitation energies, which made a thermal transition via a sloped conical intersection unlikely. We note in this connection that the second transition state found by Sakai and Nishitani and an in-plane attack of methanol can explain the formation of benzyl methyl ether without invoking a zwitterionic state.

Considerable progress has been made in the field of multireference coupled cluster (MRCC) theory.¹²⁸ A multireference Brillouin–Wigner CCSD/cc-pVTZ study of the Bergman reaction was carried out by Pittner and co-workers¹⁰⁰ who obtained an activation and reaction enthalpy at 298 K of 32.7 and 12.9 kcal/mol (see Table 1), respectively, thus revealing the necessity of including T excitations at the CC level of theory. MR CID(+Q)/cc-pVTZ (Davidson correction for the quadruple effects to obtain size consistency) calculations yielded better results (29.4 and 10.3 kcal/mol).¹⁰⁰

Singlet–triplet splittings for the three benzyne have been calculated using either Mukherjee multireference CCSD (MkCCSD),¹²⁹ general-model-space state-universal CCSD (GMS-SU-CCSD),¹³⁰ or

internally contracted (ic) MRCCSD theory.¹³¹ By including complete basis set corrections obtained for CCSD and zero-point vibrational energy corrections obtained for CCSD(T),¹²⁹ a reduced MRCCSD(T) result of 2.1 kcal/mol at the CCSD(T) geometry of *p*-benzyne was obtained for the singlet–triplet splitting. The icMRCCSD led to a value of 1.6 kcal/mol, which would be increased by the triple excitations thus approaching the experimental value of 3.8 ± 0.3 kcal/mol.⁴⁴ Evangelista and co-workers estimated the error made in their calculation to be 1.5 kcal/mol thus yielding 3.9 kcal/mol for the singlet–triplet splitting in *p*-benzyne.¹²⁹

MR-CISD and MR-averaged quadratic coupled cluster (MRAQCC) theory was used to determine the vertical excitation energies of valence and Rydberg states of *p*-benzyne. Excited states of *p*-benzyne have also been calculated with the GMS-SU-CCSD approach and compared with Mk-CCSD as well as EOM-CCSD results.¹³⁰

In summary, multireference CC methods are appealing methods for an accurate description of the Bergman cyclization; however, the calculations published so far have not reached this objective since the use of large basis sets and the calculation of geometries and vibrational frequencies at this theoretical level are not yet routine.

TARGET-SPECIFIC ENEDIYNE ANTITUMOR DRUG CANDIDATES

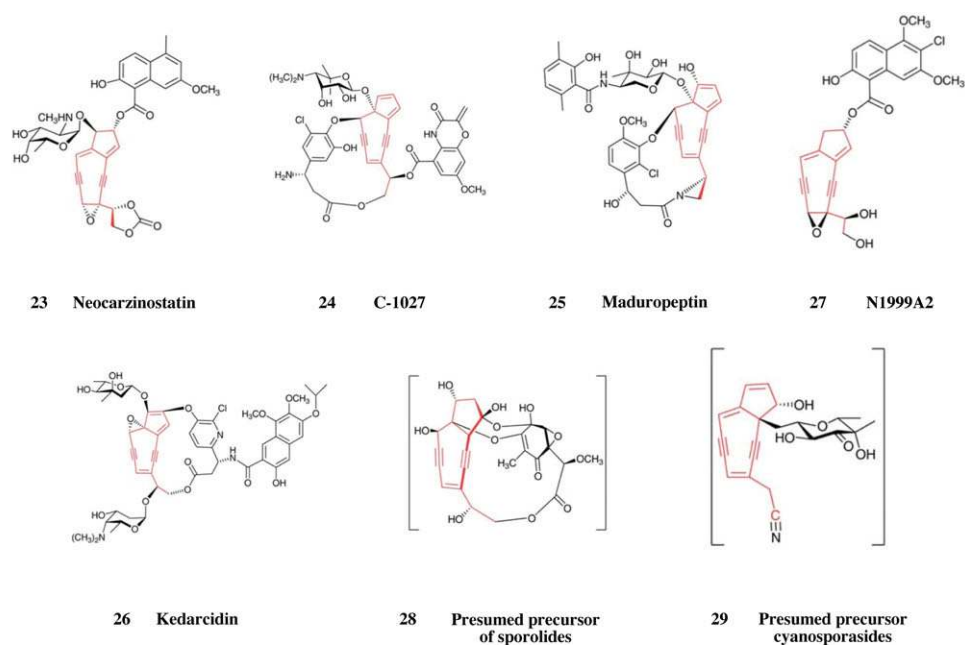
Enediynes are secondary metabolites, which are mainly produced by soil and marine microorganisms.^{28,36,132} The first structures of natural enediynes were reported in the mid-1980s.^{4–6,8,18,133,134} They are masterpieces, designed by nature to protect microorganisms against toxic bacteria and viruses. Natural enediynes show potent antibiotic and antitumor activities with a cytotoxicity comparable to or even higher than that of any known microbial metabolite.^{32,34,135–137} Up to date, ca. 40 different natural enediynes have been found.²⁸ Some commonly known enediynes^{133,134,138–148} are summarized in Table 3 and Figure 11(a) and (b). All natural enediynes possess an unsaturated core containing two alkyne units conjugated with a double bond. This core is embedded into either a 9- or 10-membered ring, and the whole unit (given in blue and purple in Figure 11(a) and (b) is often called the *enediyne warhead* because it is responsible for the biological activity of the natural enediyne. The warhead is connected to a docking unit, which helps the compound to dock into the minor groove

of DNA. Furthermore, there is a triggering device, which, if appropriately stimulated by environmental factors, triggers the warhead to undergo a Bergman cyclization. Warhead, triggering device, and docking unit are indicated in Figure 11(b) for calicheamicin.

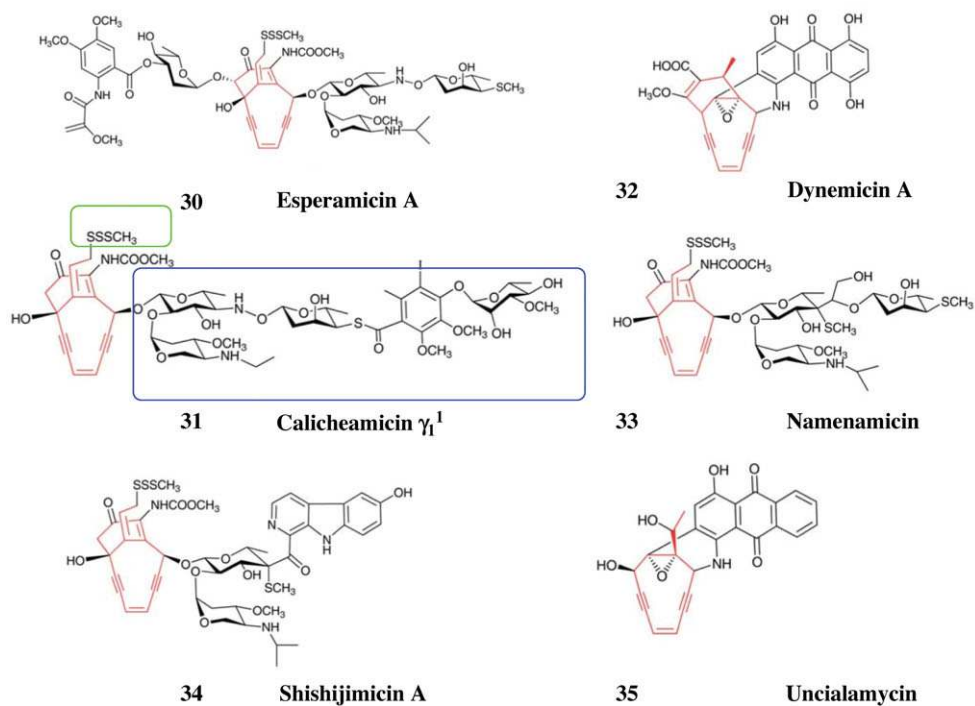
9-membered ring enediynes (see, e.g., molecules 23–29 in Table 3 and Figure 11(a)) are highly strained, and therefore are only stable if they are bound to an apoprotein.⁶³ While enediynes incorporated in a 10-membered ring are stable enough to be isolated,¹³⁷ the 9-membered ring enediynes without apoprotein undergo spontaneous cycloaromatization leading to the exclusive isolation of aromatized derivatives.⁶³ This applies to neocarzinostatin (23), C-1027 (24), maduropeptin (25), kedarcidin (26), and the precursors of sporolides (28) and cynaosporasides (29). The only known stable 9-membered ring enediyne without apoprotein is N1999A2 (27).¹⁶⁵ The enediynes included in a 10-membered ring (see, e.g., molecules 30–35 in Table 3 and Figure 11(b)) can be divided into (i) enediynes containing a sugar moiety (esperamicin (30), calicheamicin (31), name-namicin (33), shishijimicin (34)) and (ii) enediynes containing an anthraquinone moiety (dynemicin (32), unialamycin (25)). The total synthesis of the naturally occurring enediynes was actively pursued in the 1980s and 1990s by organic chemists inspired by the unusual and diverse structures of these compounds. For more detailed discussions, the reader may refer to recent review articles^{29,61,62,166} and the original literature cited in Table 3.

Apart from the many challenges caused by the total synthesis of naturally occurring enediynes, there is also the challenge of understanding how nature created their structure, i.e. how one can reconstruct their biosynthesis.^{32,167} Townsend and co-workers investigated the function of the polyketide synthases responsible for the “programmed” synthesis and regioselective cyclization of linear precursors.^{168–170} This led to new insights into how the polyketide synthases are involved in the biosynthesis of calicheamicin. In addition, their research shed light into the divergence to 9- or 10-membered natural enediynes, which results, according to the authors, from the action of one or more accessory enzymes acting in concert with the enediyne polyketide synthases.

The gene clusters for 23, 24, 25, 31, and 32 have been cloned and sequenced¹⁶⁷ thus providing the basis for understanding nature’s means to create such complex, exotic molecules. Sequencing of the gene clusters could confirm the polyketide origin of the enediyne warheads. Aromatic moieties are derived either from polyketides or primary metabolic intermediates, whereas the unusual sugars are a result



(a) Nine-membered enediynes.



(b) 10-Membered enediynes.

FIGURE 11 | Naturally occurring enediynes. For each enediyne, the warhead is given in red. For calicheamicin γ_1^1 , the docking (blue box) and the triggering device (green box) are also indicated.

TABLE 3 | Some Representative Natural Enediynes.

Compound	Biological Origin	First Structure	Total Synthesis
9-membered ring			
Neocarzinostatin (23)	<i>Streptomycescarzinostaticus</i> (terrestrial)	1985 ¹³³	1985 ¹⁴⁹
C-1027 (24)	<i>Streptomycesglobisporus</i> (terrestrial)	1991 ¹³⁸	1985 ¹⁵⁰
Maduropeptin (25)	<i>Actinomadura madurea</i> (terrestrial)	1994 ¹³⁹	1985 ¹⁵¹
Kedarcidin (26)	<i>Actinomycete</i> L585 – 6 (terrestrial)	1997 ¹⁴⁰	1985 ¹⁵²
N1999A2 (27)	<i>Streptomyces</i> sp. AJ9493 (terrestrial)	1998 ¹⁴¹	1985 ¹⁵³
Sporolides ^b (28)	<i>Salinisporatropica</i> (marine)	1985 ¹⁴²	1985 ¹⁵⁴
Cyanosporasides ^b (29)	<i>Salinisporapacifica</i> (marine)	1985 ¹⁴³	1985 ¹⁵⁵
10-membered ring			
Esperamicin (30)	<i>Actinomadura verrucosospora</i> (terrestrial)	1985 ¹³⁴	1985 ¹⁵⁶
Calicheamicin (31)	<i>Micromonospora echinospora</i> ssp. <i>calichensis</i> (terrestrial)	1985 ¹⁴⁴	1985 ^{157–159}
Dynemycin (32)	<i>Micromonospora chersina</i> (terrestrial)	1985 ¹⁴⁵	1985 ^{160, 161}
Namenamicin (33)	<i>Polysyncraton lithostrotum</i> (marine)	1985 ¹⁴⁵	1985 ¹⁶²
Shishijimicin (34)	<i>Didemnum proliferum</i> (marine)	1985 ¹⁴⁷	1985 ¹⁶³
Uncialamycin (35)	Unknown (marine)	1985 ¹⁴⁸	1985 ¹⁶⁴

of a modification of common sugars carried out by special enzymes. It seems that all building blocks are assembled separately and joined together in the final stage with the help of regioselective enzymes; however, details are not understood yet. There are also open questions concerning the determinants leading to a 9- versus 10-membered ring in the biosynthesis of the enediyne warhead.

Although structurally diverse, all naturally occurring enediynes share the same, unique mode of action leading to apoptosis caused by DNA cleavage. Enediynes intercalate into chromosomal DNA in a sequence-specific fashion.^{34, 132, 136} The specific chemistry of triggering and docking device of an enediyne fine-tunes its biological activity, which is driven by the enediyne warhead and which determines its cytotoxicity. Triggered by an environmental change such as thiol activation or ultraviolet light, the enediyne core undergoes a Bergman cyclization to yield a benzenoid biradical. The biradical abstracts hydrogen atoms from DNA generating in this way a carbon-centered radical in the ribose part. In the presence of O₂, the DNA will undergo facile double- or single-stranded cleavage through an oxidative radical mechanism causing cell death.^{18, 171}

The research on enediynes had a strong impact on the development of antitumor drugs in so far as it followed a rational design strategy based on nature rather a trial and error approach.^{32, 34, 135–137} At an early stage, it became clear that the bioactivity of the enediynes could be used to destroy tumor cells and this expectation inspired and challenged the synthesis of bioactive enediynes.^{33, 61, 166, 172}

Much of the early work on natural enediynes overlooked the fact that they are highly toxic because they do not discriminate between normal and tumor cells, i.e. natural enediynes are not target specific. There are two basic approaches for solving the toxicity problem: (i) the design of artificial target-specific enediyne mimics and (ii) the modification of natural enediynes to make them target specific. If the modifications are constrained to the warhead, the natural docking and triggering device will not be affected and can be used. In any case, one has to develop a strategy how the enediyne shall differentiate between normal and cancer cells.^{173–177}

The Design of Artificial Target-Specific Enediyne Mimics

Different strategic routes have been pursued for the rational design path of pH-triggered enediynes, where attempts have been inspired by the triggering mechanisms applied by nature (for a recent summary, see Basak and co-workers³³). Common to the four strategic routes A, B, C, and D (see Figure 12) discussed in the following is the idea that a nonreactive precursor is converted by a pH change (acidic or basic medium) into an enediyne or enyne-allene. In the case of a change toward a more acidic medium, the bioactivity of the enediyne mimic is in line with the fact that cancer cells are slightly acidic.¹⁷⁸ However, there is only a gradual lowering of the pH in the cancer cell compared to that in the normal cell (see below). In so far those strategies, which are based on a lowering of the pH, have to be scrutinized whether the lowering required is beyond that what is possible

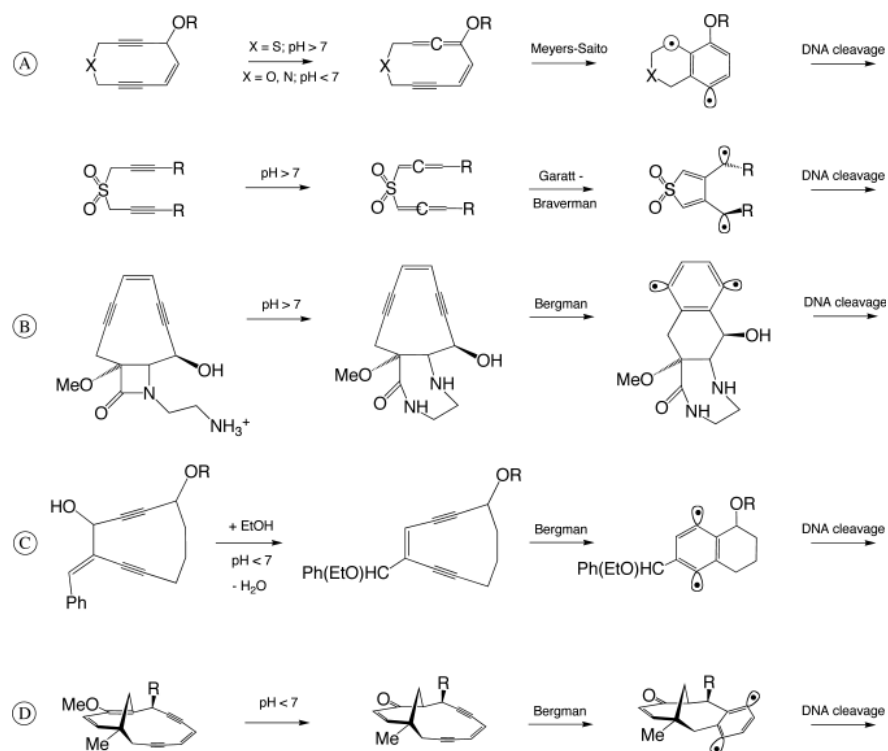


FIGURE 12 | Suggested strategies for biradical formation of an enediyne mimic or related compounds via a precursor at ambient conditions to yield DNA cleavage.

in the cancer cell. As for the alternative strategy (increasing the pH), a direct use as a potential anti-tumor drug is difficult to foresee. This has to be kept in mind when evaluating the many enediyne mimics synthesized.

Route A: Enyne-Allene Principle

This strategic route makes use of the fact that the barrier of the Myers-Saito cyclization (21.8 kcal/mol, Table 2) is lower than that of the Bergman cyclization (28.7 kcal/mol, Table 1). When triggered by a change in pH, a stable precursor isomerizes to an enyne-allene (see A in Figure 12), which performs a Myers-Saito rearrangement under physiological conditions. Two examples are given in Figure 12. A sulfide with two propargyl groups embedded in a 10-membered ring rearranges under basic condition. The corresponding aza and oxo analogues carry out the cyclization under acidic conditions.¹⁷⁹ Shibuya and co-workers¹⁸⁰ designed enediyne model compounds, which isomerize to enyne-allenes and generate toluene biradicals under acidic conditions. Tuesuwan and Kerwin¹⁷² synthesized 4-aza-3-ene-1,6-diyne systems with pH-dependent DNA-cleavage activity.

Interesting in this connection is the Garatt-Braverman cyclization, which involves a double allene

reaction with subsequent biradical formation.¹⁸¹ As an example, the rearrangement of a bispropargyl sulfone is shown in Figure 12, which isomerizes in alkaline media to an allenic sulfone and then transforms into a bioactive biradial at ambient temperatures.¹⁸¹

Route B: Locking Principle

The strategy of this route is to stabilize the enediyne by fusion to a locking device (e.g., the four-membered ring shown in B, Figure 12) such as an epoxide as in dynemicin¹⁴⁵ (Figure 11(b)). If equipped with a pH-sensitive trigger, the locking device opens in an acidic medium and sets a reactive enediyne free. The example shown in Figure 12 includes a substituted β -lactam, which forms an ammonium ion in acidic medium, but requires then a basic medium to open the lactam ring by in an intramolecular, nucleophilic substitution to a six-membered ring, which activates the Bergman reaction in the annulated 10-membered ring.^{33,182}

Route C: Activation of Prodrug Principle

The strategic principle of this route is based on the *in situ* generation of the enediyne through an allylic

rearrangement, which is triggered in acidic medium. The serendipitous finding that maduropeptin chromophore (25), when being extracted with methanol, transforms into a reactive enediyne via an intramolecular nucleophilic attack of the alcohol¹³⁹ has motivated this synthetic route. It has been applied, for example, by Dai and co-workers¹⁸³ as shown in Figure 12. A related strategy is the *in situ* generation of an enediyne via β -elimination.¹⁸⁴

Route D: Rehybridization Principle

Calicheamicin¹³⁴ and esperamicin¹⁴⁴ are triggered by a conversion of an sp^2 -hybridized carbon into a sp^3 -hybridized carbon. The rehybridization strategy has been utilized for pH triggering. For example, Semmelhack and co-workers¹⁸⁵ designed enol-enediynes with a CC double bond at a bridgehead position (see route D in Figure 12). Conversion of the enol into the corresponding keto form under acidic conditions leads to the desired rehybridization. The resulting ketone undergoes Bergman cyclization at physiological conditions.

Modification of Natural Enediynes

The modification of the warhead of the naturally occurring enediynes has been sparsely pursued so far. This more “top-down” approach implies the detailed understanding of the mechanism leading to biological activity of a natural enediyne. In addition, one has to investigate all changes in the biological activity of the enediyne upon altering the warhead. This is a tedious task with an uncertain outcome when based on chemical synthesis. Therefore, computational chemistry plays an important role since it can be used for a better understanding of the mechanism leading to the bioactivity of natural enediynes as well as the monitoring of changes in this mechanism upon modification of the warhead. In view of the size of the natural enediynes, molecular mechanics (MM) investigations have focused on their conformational flexibility.^{137,177} MM calculations however can say little with regard to the biological activity of a natural enediyne because this involves bond formation/cleavage, which can only be described utilizing quantum chemical means. There are a few quantum mechanical (QM) and QM/MM (quantum mechanics combined with molecular mechanics) studies of natural enediynes, which will be considered first before the work on a possible modification of their warheads is reviewed.

Computational Investigation of Natural Enediynes

Extensive work on dynemicin and calicheamicin and their reactions has been published by Kraka, Cremer and co-workers who studied the docking, triggering, cyclization, and H-abstraction mechanism inside and outside DNA by appropriate QM and QM/MM methodologies, where the QM part was based on BS-UDFT calculations with the B3LYP hybrid functional.^{59,173–175}

Dynemicin A, when locked in its untriggered form via the epoxide unit is predicted to undergo the Bergman cyclization with the extremely high barrier of 52 kcal/mol.⁵⁹ When the epoxide ring opens after appropriate triggering, the energy barrier is reduced to 17.9 kcal/mol with the consequence that H-abstraction at ambient temperature becomes possible. If triggering and biological activity of dynemicin A are investigated both inside and outside the minor groove of a duplex 10-mer B-DNA sequence d(CTACTACTGG)-d(CCAGTAGTAG), the importance of a fine-tuning of docking and triggering becomes obvious. Triggering happens in the minor groove in an insertion rather than intercalation mode by NAPDH (nicotinamide adenine dinucleotide phosphate), thiols, or other reducing agents, which are able of attacking a protruding part of the molecule. Triggering is a highly exothermic process that, despite of energy dissipation, should provide a sufficient excess of energy for dynemicin to carry out the Bergman reaction.¹⁷³ An important finding of the quantum chemical investigation was that the activity-relevant docking mode is an edge-on insertion into the minor groove, whereas the intercalation between two base pairs, although leading to larger binding energies, excludes a triggering of dynemicin A and the development of its biological activity, as shown in Figure 13.¹⁷³

An insertion–intercalation model was developed that can explain known experimental observations made for dynemicin, especially the observation of the high ratio of single-strand to double-strand scission.¹⁷³ In a follow-up study on dynemicin,¹⁷⁵ a state-of-the-art QM/MM calculation revealed that for the Bergman and retro-Bergman cyclization steps of dynemicin the explicit consideration of environmental factors such as the receptor DNA, the solvent water, and charge neutralization by counterions has only minor effects on the energetics of the cyclization, which is obviously due to the cyclic structure of the enediyne investigated. In this case, the energetics is predominantly determined by QM (electronic) effects. This makes a cost-effective

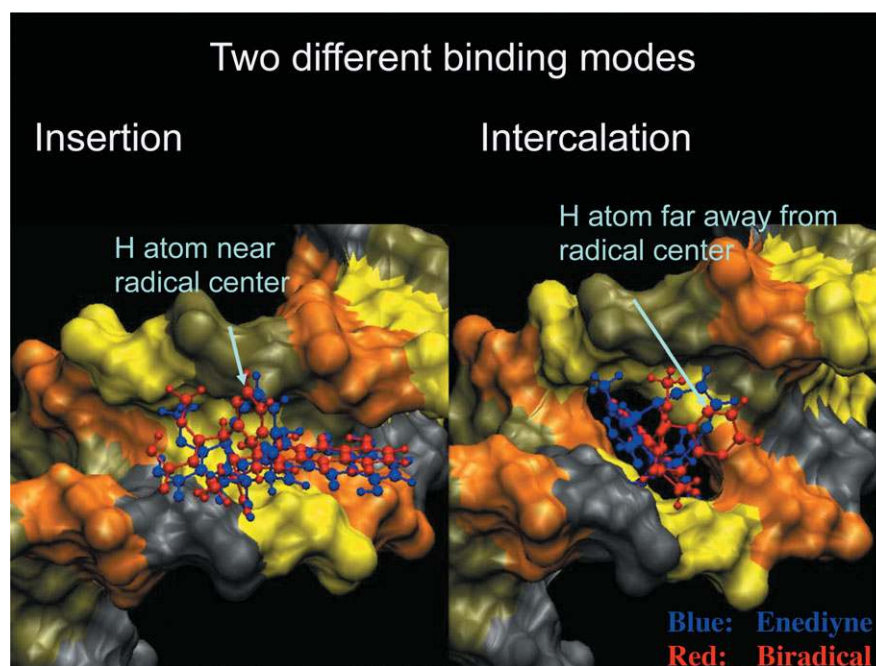


FIGURE 13 | Docking of dynemicin into the minor groove of DNA. (a) Insertion and (b) intercalation. (Reproduced from Ref 173. Copyright 2005, American Chemical Society.)

decoupled QM+MM approach useful for the investigation of natural enediynes.^{173,174} For the retro-Bergman cyclization, which involves the acyclic isomer of dynemicin, a lowering of the barrier from 31.3 kcal/mol (gas phase) to 23.7 kcal/mol (inside the minor groove) was found. The lowering of the barrier is reflected by a decrease of the critical distance between atoms C1 and C6 from 4.29 to 3.42 Å.¹⁷⁵ The reduction of the barrier is a result of a stabilization of the transition state, which is caused by an increased dipole moment and hence stronger electrostatic interactions with the environment. This finding proves the possibility of using acyclic enediynes for drug design if properly anchored in the minor groove.

The triggering and the Bergman cyclization of calicheamicin **31** outside and inside the minor groove of the duplex 9mer-B-DNA sequence d(CACTCCTGG)-d(CCAGGAGTG) was also investigated applying the QM/MM methodology.¹⁷⁴ In contrast to dynemicin, the environment plays a decisive role for the biological activity of calicheamicin, which became clear with the help of QM/MM investigations. Only when calicheamicin is confined to the space of the minor groove triggering leads to a conformation, which performs the Bergman cyclization at ambient temperature whereas outside the DNA calicheamicin is stable. The quantum chemical calculations confirmed the high toxicity of **31**, which performs a DNA double strand scission. There have been investigations on esperamicin; however, in these cases

only parts of the molecule were quantum chemically calculated.¹⁸⁶

Modification of the Warhead of Natural Enediynes: The Role of Heteroenediynes

Any modification of the warhead must have the objective to make the enediyne target specific, i.e. it should attack the tumor rather than the normal cell. This implies that the enediyne must be sensitive to the differences between normal and tumor cell, of which there exist only a few:¹⁷⁸

i. There is a reduced blood flow in the cancer cell compared to the normal cell. ii. Also the oxygen content is strongly reduced in the cancer cell. iii. Because of the increased nutrition (energy) demand of a tumor cell, glycolysis is strongly enlarged. iv. Owing to the increase in glycolysis, the pH of a cancer cell is lowered to 6.2–6.6 compared to that of the normal cell (pH: 7.0–7.2).^{187,188}

There is little chance of exploiting (i)–(iii). However, the lowering of the pH in the tumor cell speaks for the incorporation of a pH sensor into the enediyne warhead. Along these lines, Kraka and Cremer developed an antitumor-enediyne drug principle.^{189–191} Clearly, a change in the pH by maximally one unit requires an extremely sensitive chemical pH-measuring device although MCT (monocarboxylate transporters) inhibitors, hyperthermia, or hyperglycemia may lower the pH of the tumor cell to even 5.5 (even lower pH values lead to cell

TABLE 4 | Energetics of the Bergman Cyclization of (Z)-aza-hex-3-ene-1,5-diyne (**37**) to the Corresponding Biradical **38** and the Protonated Form of **37** (**39**) to the Corresponding Protonated Biradical **40**

Method/Basis Set	$\Delta H^\ddagger(37-38)$	$\Delta H^\ddagger(38-37)$	$\Delta_R H$	T-S	Ref.
BS-UPW91/cc-pVDZ	14.5	29.0	-14.5	14.0	195
BS-UB3LYP/6-31+G(3df,3pd)	23.8	35.9	-12.1	9.1	56
CCSD(T)/cc-pVDZ	17.5	28.2	-10.7	12.9	195
BD(T)/cc-pVDZ	17.4	27.2	-9.7	11.6	195
CASSCF(6,6)/6-31G(d) ^a	33.2	32.7	0.5	6.3	102
CASPT2(10,10)/cc-pVDZ	16.3	36.1	-19.8	14.1	195
CASPT2(12,11)/ANO-S	15.1	27.6	-12.5		104
CASMP2(6,6)/6-31G(d) ^a	27.7	39.8	-12.1	8.2	102
Experimental	22.5 ± 0.5		na	na	102

Method/basis set	$\Delta H^\ddagger(39-40)$	$\Delta H^\ddagger(40-39)$	$\Delta_R H$	T-S	Ref.
BS-UPW91/cc-pVDZ	18.3	25.2	-6.9	4.3	195
BS-UB3LYP/6-31+G(3df,3pd)	27.9	27.0	-0.9	3.8	56
CCSD(T)/cc-pVDZ	19.9	50.5	-30.6	29.8	195
BD(T)/cc-pVDZ	19.9	25.8	-7.0	5.6	195
CASSCF(6,6)/6-31G(d) ^a	32.5	30.4	2.1	2.2	102
CASPT2(10,10)/cc-pVDZ	18.2	33.3	-15.1	5.6	195
CASMP2(6,6)/6-31G(d) ^a	29.1	40.9	-11.8	2.7	102

^a ΔE values at 0 K.

death^{192–194}). It was obvious that a pH sensitive group must be a heteroatom such as nitrogen, which, when incorporated into the enediyne framework and protonated, leads to a varying energetics for the Bergman cyclization. Different heteroenediyne systems including N-containing enediynes, related N,C-dialkynyl amides, and amidines were computationally tested for their suitability as pH sensors. As an example, the energetics of (Z)-3-aza-hex-3-ene-1,5-diyne (**37**) is summarized in Table 4, for which, beside the experimental investigation¹⁰² of the activation enthalpy, a larger number of quantum chemical data were published.

As in the case of the parent enediyne **1**, BS-UDFT, if carried out with a large basis set (diffuse functions for the heteroatom), and avoiding a double counting of correlation effects by using a hybrid functional for the broken symmetry approach (see section *Broken Symmetry UDFT Description of p-Benzynes*) leads to reasonable results. The CCSD(T) and BD(T) calculations of Cramer¹⁹⁵ suffer from the use of DFT geometries, whereas both CASSCF and CASPT2 are unreliable, which is a consequence of the enhanced difficulties in defining a balanced active space. As was pointed out by Kraka and Cremer¹⁹¹, there is, beside through-bond interaction, also a(n) (anomeric) three-electron delocalization involving the N electron lone pair and the adjacent C atom with the unpaired electron. Hence, a (14,13) or even (22,21) active space is needed for the CASPT2 description of **37**.

The BS-UDFT results suggest, in line with the experimental observations, that incorporation of an N atom into the enediyne framework as in **37** leads to a lowering of the barrier and an increase of the exothermicity of the reaction (ΔH^\ddagger : 23.8 kcal/mol; $\Delta_R H$: -12.1 kcal/mol). The use of **37** in the warhead of a natural enediyne to make it pH sensitive could imply the following advantages: (i) The singlet–triplet splitting (S-T in Table 4) is 9.1 kcal/mol and by this indicative of a biradical with low reactivity, which is a desirable effect because **37** should not react in the neutral medium of a normal cell. (ii) Also favorable is that protonated biradical **40** does not convert back to **37** at room temperature (activation enthalpy for the retro-Bergman reaction: 27.0 kcal/mol, Table 4). It would abstract an H atom from DNA, which requires 6–12 kcal/mol.^{176,196} (iii) The protonated biradical **40** should be strongly reactive in view of a S-T splitting of 3.8 kcal/mol.

Although (i)–(iii) are in favor of a warhead based on **37**, the fact that the protonated form **39** has a cyclization barrier of 27.9 kcal/mol, which makes it nonreactive at body temperature, excludes the system **37,39** to be used as pH sensor when distinguishing between normal and tumor cells.

Nevertheless, the search for suitable aza-enediynes has been continued. Kerwin and co-workers¹⁹⁷ synthesized a series of 1,2-dialkynylimidazoles. They invested the Bergman

cyclization of these compounds by experimental and computational means using DFT. Although the Bergman cyclization of these compounds proceeds at ambient temperature, they could not find a correlation between the rate of the Bergman cyclization and the cytotoxicity to A459 cells.¹⁹⁷ They concluded that there is no evidence that the cytotoxicity of these 1,2-dialkynyl-imidazoles is due to DNA cleavage via a biradical. This is in line with a large S-T gap of 9–10 kcal/mol, which was calculated. In contrast to these results, Kerwin and co-workers did find DNA cleavage via the Myers–Saito cyclization for 4-aza-3-ene-1,6-diyne systems.¹⁷²

In view of their investigation of natural enediyne and their experience with heteroenediyne, Kraka and Cremer formulated the following *seven criteria for the design of a pH-dependent, nontoxic natural enediyne*:¹⁸⁹

- i. The original, neutral enediyne must be protonated at a pH between 5.5 and 6.6.
- ii. The protonated enediyne must be kinetically stable against decomposition or rearrangement reactions other than the Bergman cyclization.
- iii. The protonated enediyne must undergo Bergman cyclization at ambient temperature.
- iv. The protonated biradical must be kinetically stable, and H abstraction must be its preferred reaction.
- v. The biological activity of the protonated biradical must be high.
- vi. The enediyne in question must be easy to synthesize.
- vii. The enediyne-based drug must possess the appropriate ADME (absorption, distribution, metabolism, excretion) properties to guarantee an optimal performance as antitumor antibiotics.¹⁹⁸

The last two criteria are difficult to assess from a chemical point of view because they imply extensive studies in pharmacology. At least with regard to (v) a rule of thumb was established on the basis of quantum chemical studies:^{102,189,191} *The biological activity of a biradical is high (low) if its singlet–triplet splitting is low (high)*. This rule follows the observation that, e.g., through-bond delocalization in *p*-benzyne reduces its biradical character, stabilizes the singlet state, and accordingly increases the singlet–triplet splitting. A strongly stabilized

singlet biradical is no longer reactive, and therefore the singlet–triplet splitting can be used as a simple indicator for the biological activity of a biradical formed by cyclization of enediyne or enyne-allene.

Another rule, also used by Kraka and Cremer, concerned the bioactivity of the enediyne at ambient temperature, which implies that the Bergman cyclization or any other biradical-producing cyclization takes place at body temperature. These authors used simple considerations based on activation free energies, rate constants, and frequency factor (activation entropy) to estimate that for a significant rate at room temperature, the activation enthalpy should not be higher than 22 kcal/mol.¹⁸⁹

Based on this experience, Kraka and Cremer designed what they called the *door-handle principle*, which is based on the idea of a nonreactive precursor with a single bond separating the alkynyl groups. Upon protonation, the enediyne unit is established and the system undergoes a Bergman cyclization (see Figure 14). Such a system could be an amide (X = O, Y = NH) or amidine (X = NR, Y = NR). Investigation of 15 molecular systems with the atom combination for X and Y shown in Figure 14¹⁸⁹ revealed that amidines are best suited for this purpose because their pK_a values make it possible that they are protonated at a pH of 5.5–6.5 and their energetics for the Bergman cyclization can be modulated by incorporation into the 10-membered ring system **53** in such a way that they fulfill requirements (i) to (v) set up by Kraka and Cremer.¹⁸⁹

The first prototype of a pH-dependent natural enediyne by replacing the enediyne moiety in dynemicin by an dialkynyl amidine warhead was suggested on the basis of QM+MM calculations.¹⁷⁶ The resulting dynemicin-amidine (DAD) is biologically not active because it forms an extremely labile singlet biradical that can no longer abstract H atoms from DNA because it rearranges immediately to a cumulene (see Figure 15). However, if protonated, it fulfills all requirements for a pH-sensitive modified natural enediyne, as is reflected by a lowering of the activation enthalpy for the Bergman cyclization from 16.7 (dynemicin A) to 11.5 kcal/mol (protonated DAD), kinetic stability of the singlet biradical formed in the cyclization reaction (retro-Bergman barriers of 20.6 and 14.9 kcal/mol), and an increased H abstraction ability of the singlet biradical in view of a S-T splitting of just 1.4 kcal/mol. In addition, DADs in general show improved docking properties in the minor groove of the duplex 10-mer B-DNA sequence d(CTACTACTGG)·d(CCAGTAGTAG) throughout the triggering and Bergman cyclization process. Unpublished work reveals that with an

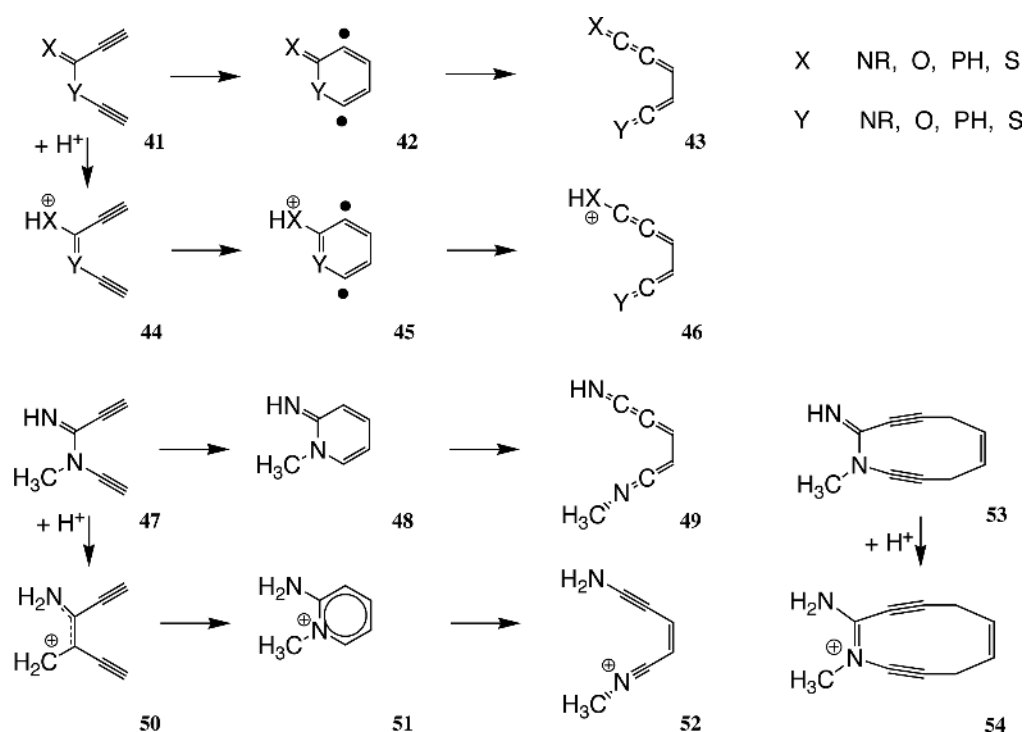


FIGURE 14 | The door handle principle of Kraka and Cremer illustrated for amidines and protonated amidines. (Reproduced from Ref 189. Copyright 2000, American Chemical Society.)

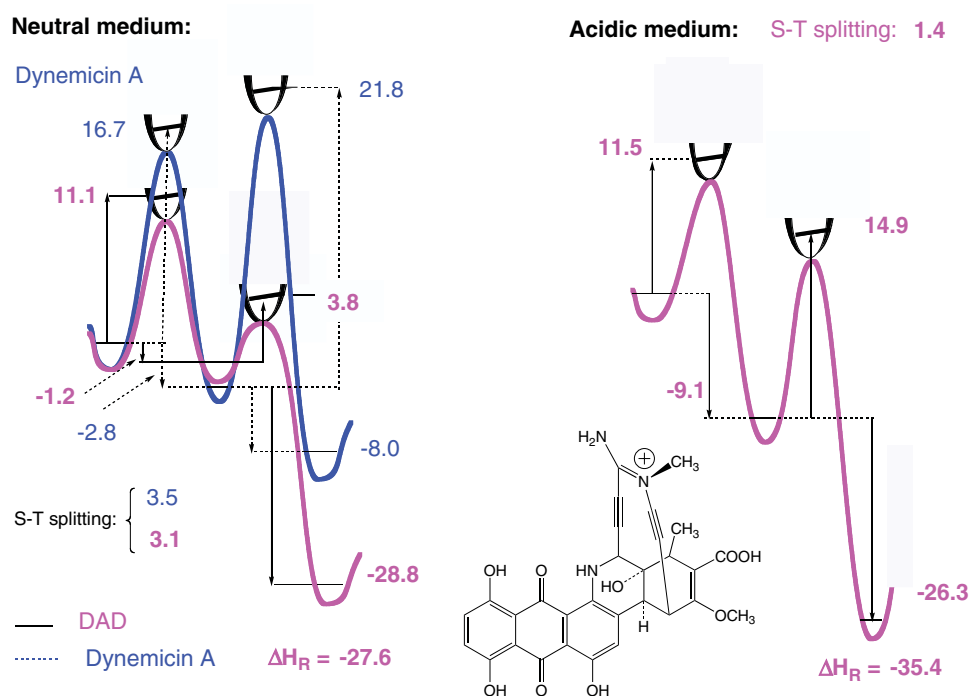
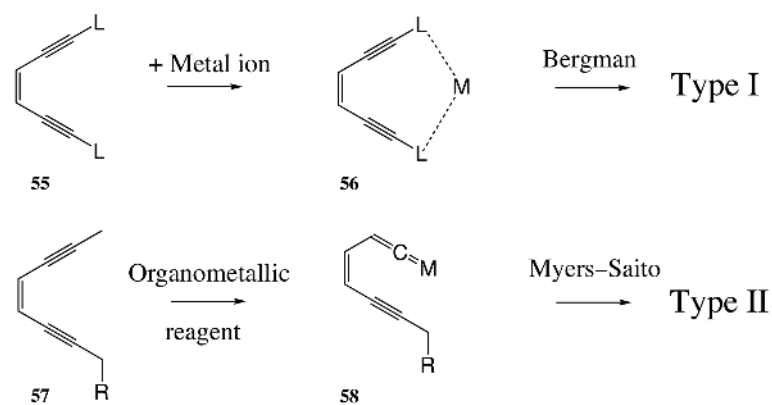
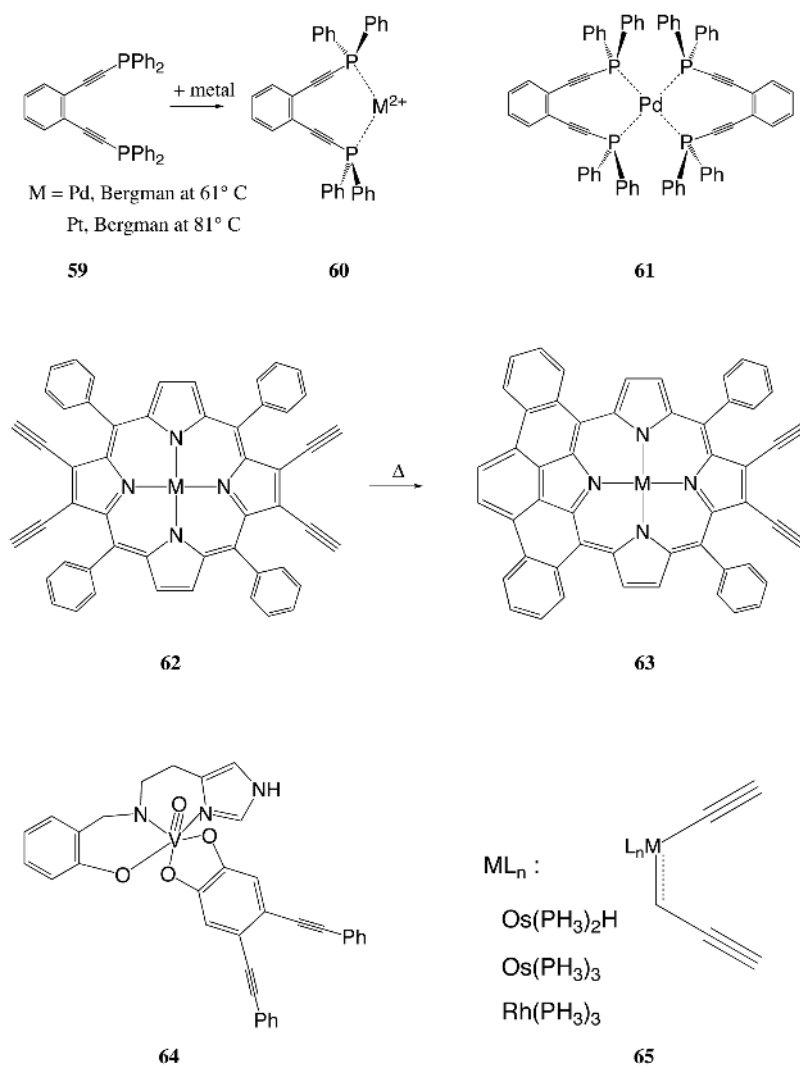


FIGURE 15 | Energetics of dynemicin (blue) versus dynemicin-amidine (DAD; purple). (Reproduced from Ref 176. Copyright 2008, American Chemical Society.)



(a) Type I and II reactions



(b) Examples of metalloenediynes

FIGURE 16 | Metalloenediynes investigated to modulate the energetics of the Bergman reaction.

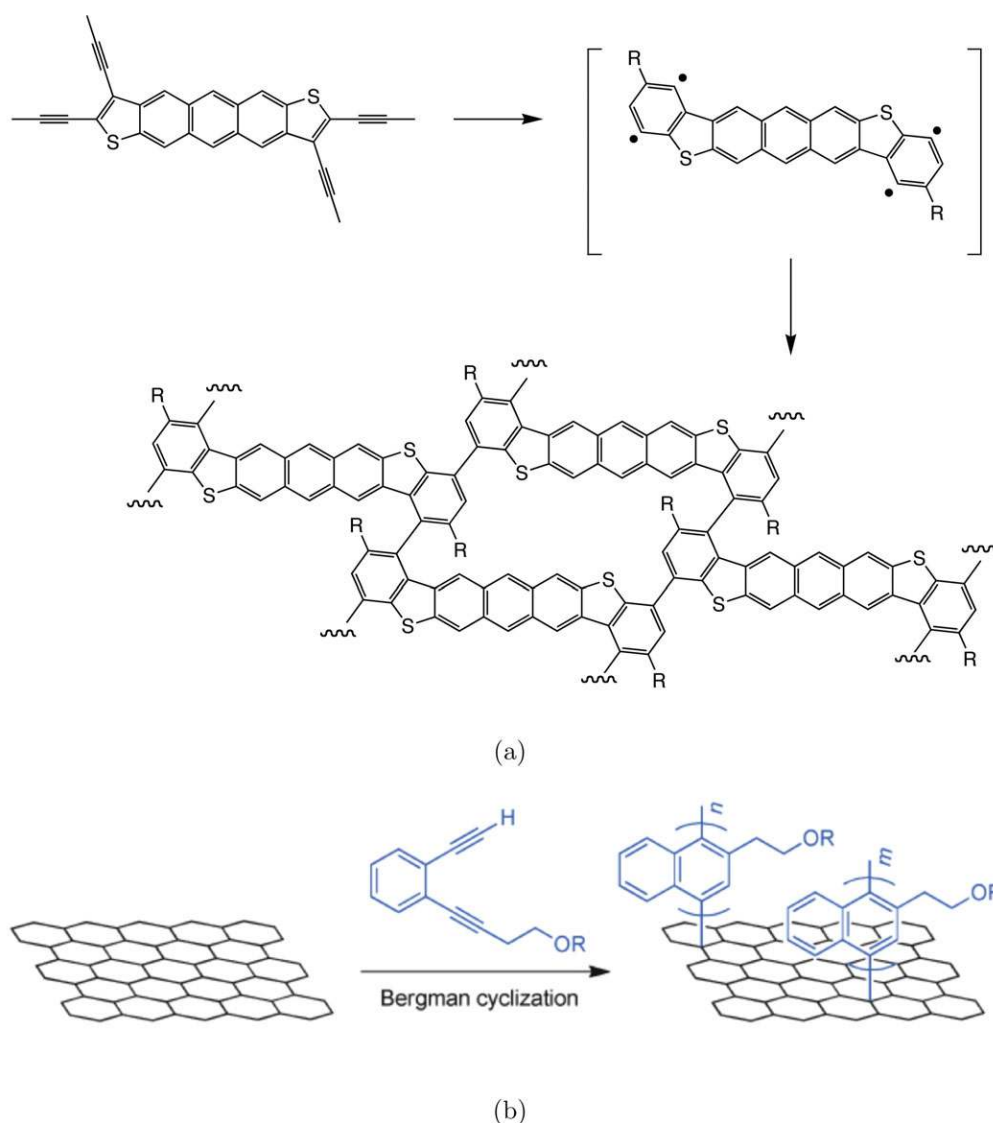


FIGURE 17 | Polymerization of enediynes.

appropriate choice of the amidine substituents the pK_a of a DAD can be fine-tuned to a point that the molecule is protonated in the desired pH range of 5.5–6.5. In this way, an effective anticancer drug based on a nontoxic, pH-sensitive modified natural enediyne can be realized. This work showed also that modification of the warhead is limited. In the case of dynemicin, it does not change the docking properties whereas for calicheamicin it does because of the space requirements of the amidine and the different, tighter docking mode of calicheamicin.¹⁷⁴

METALLO-ENEDIYNES

The use of metals for a modulation of the Bergman cyclization has become an emerging research

field.^{28,30,33,51,199} In general, metal sites offer additional structural flexibilities over their carbocyclic or acyclic organic analogues, which contributes to their intriguing Bergman cyclization reactivity. As shown in Figure 16(a), there are two basic modes of action.

Type I; Eneidyne **55** bind via their ligands **L** to a metal ion M^{n+} thus forming a metal-chelated ring **56**, which undergoes the Bergman cyclization.

Type II; Organometallic reagents promote the isomerization of enediyne **57** to enyne-allene **58**, followed by a Myers–Saito cyclization.

In both cases, significant variations in the Bergman cyclization or Meyers–Saito reaction result provided the right choice of the metal is made. Some representative examples will be discussed in the following.

1,2-Bis(diphenyl-phosphino)ethynyl)benzene **59** undergoes the Bergman cyclization at 243°C, as measured by differential scanning calimetry.²⁰⁰ Complexation with Pd(II) or Pt(II) (see **60** in Figure 16(b)) lowers the barrier considerably so that cyclization takes place at 61° and 81°, respectively. In contrast, the thermal activity of **61** is strongly reduced although both complexes share the same ligand. The main difference is the oxidation state of Pd, which is II in **60** and 0 in **61**. Based on these findings, Zaleski and co-workers¹⁹⁹ have recently designed redox-activated metalloenediyne prodrugs leading to a new strategy for potential dual-thread metalloenediyne therapeutics.

A promising application of metallo-enediyne also exists in the field of photodynamic therapy. Zaleski and co-workers²⁰¹ synthesized the vanadium (V) complex **64** (Figure 16(b)) with strong ligand-metal charge transfer transitions in the near infrared region caused by the low redox potentials of the highly valent vanadium center and easily oxidizable metal bonds. The Bergman cyclization is activated photochemically using laser light of the wavelength 785 and 1064 nm, respectively, which correspond to wavelengths that ensure enhanced tissue penetration. Recently, the spin-state control of thermal and photochemical Bergman reaction was reported for Pt(II)-dialkynylporphyrin **62**.²⁰² The thermal Bergman cyclization reactivity of **62** reveals a surprising reduction in the temperature at which the piconoporphyrin product is formed when compared to Zn(II) derivatives or the metal-free **62**.²⁰³ Hoffman and co-workers²⁰⁴ investigated the Bergman cyclization of osmaenediynes and rhodaenediynes **65** (Figure 16(b)). Their computational results suggest a potentially significant decrease in the energy of activation, when a 14-electron metal fragment replaces a four-electron carbon, which could lead to new metallo-enediyne compounds for drug design.

CURRENT DEVELOPMENTS IN ENEDIYNE CHEMISTRY AND THE FUTURE

Enediyne had an important impact on organic chemistry. Today, one makes strategical use of the Bergman cyclization in organic synthesis.^{20,21,30,31,51} To some extent, this holds also for the Meyers–Saito, Schmittel,^{25,50} or the Garatt–Braveman reaction.²⁰⁵ The Bergman cyclization had also its impact on the closely related Cope rearrangement.^{13,206} The work on heteroenediynes and their nucleophilic cyclization

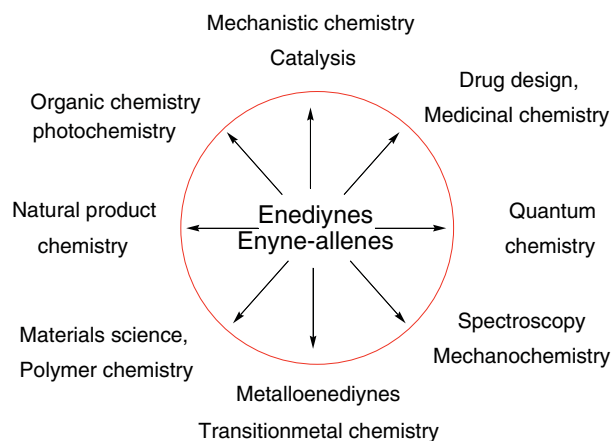


FIGURE 18 | The impact of enediyne and enyne-allenes on chemistry.

has turned out to be a promising method in heterocyclic synthesis.³¹

Interesting and relatively new are the studies on a photochemical triggering of the Bergman cyclization as, for example, in the case of the benzannulated cyclodeca-3,7-diene-1,5-diynes.²⁰⁷ Based on these observations, Popik and co-workers³⁵ designed photoswitchable enediyne, which are stable in the dark, however undergo a cycloaromatization reaction to produce *p*-benzyne biradicals after irradiation with light of an appropriate wavelength. Alabugin and co-workers^{208,209} recently designed hybrid molecules combining photoactivated aryl alkynes and a dicationic lysine moiety, which efficiently performs double-strand DNA cleavage. Catalyzed enediyne reactions^{210–214} or reactions, in which the enediyne acts as a catalyst, e.g., for the synthesis of chiral products,²¹⁵ are also a novelty. Recently, enediyne have been used in gold chemistry for a new entry to domino reactions. Au attacks the triple bond to form a π -complex, which rearranges to form σ -bonded Au compounds. Hashmi and co-workers discovered that terminal 1,2-dialkynylarenes undergo an unexpected cyclization hydroarylation reaction toward naphthalene derivatives. The regioselectivity of the reaction can be controlled by tuning the gold catalyst.²¹⁴ Another peculiarity of enediyne chemistry is the (so far not successful) use of the enediyne core as a potentially useful mechanophore.²¹⁶

Finally, it has to be mentioned that enediyne have found a special role in materials science and polymer chemistry.²¹⁷ Although still in its infancy, the Bergman cyclization has already proven a valuable tool in polymer chemistry where it is applied in a twofold way: (i) The highly reactive *p*-benzynes generated by the Bergman cyclization can

undergo polymerization acting either as monomers or initiators of other vinyl monomers thus leading to carbon-rich materials, e.g., glassy carbons and carbon nanotubes. In the case of homo-polymerization, high-density polymers with excellent thermochemical properties are obtained (see Figure 17(a)).²¹⁸ (ii) The Bergman cyclization can also be used to covalently modify carbon materials such as graphene (see Figure 17(b)), and in this way improve their poor solubility and dispersibility.²¹⁹

In summary, the chemistry of enediyne has affected many fields of chemistry, for which Figure 18 provides an overview. There were times of enhanced and reduced interest in enediyne chemistry, and there were times where the work in this field was considered as superfluous. Even then, researchers from some times diametrically different fields in chemistry have proved these opinions as being wrong. In the year 2013, one can say that after more than 40 years, enediyne chemistry has still much to offer.

ACKNOWLEDGMENTS

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