ELECTRONIC EFFECTS ON THE BERGMAN CYCLISATION OF ENEDIYNES. A REVIEW

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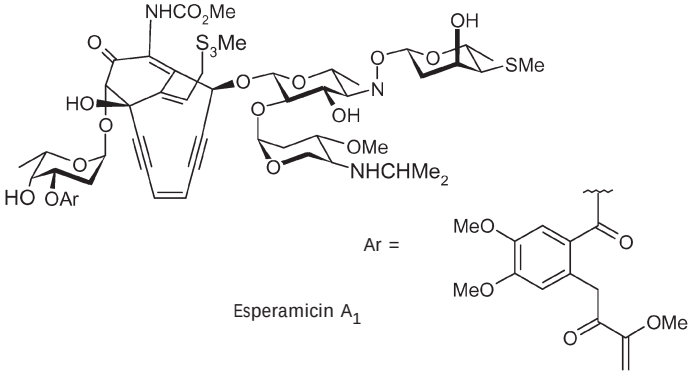
Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday.

The thermal cyclisation of enediynes to benzene-1,4-diyl diradicals (Bergman cyclisation) is affected by geometrical and electronic conditions. While the effect of ring strain or conformational constrains on the cyclisation temperature has been investigated in detail, electronic contributions have been less studied. Often geometrical and electronic contributions cannot be clearly distinguished. In most cases metal ion chelation does involve both. In this review we have summarised clear-cut observations of electronic substituents effects on the thermal enediyne reactivity. The effects of substituents in the vinylic and terminal alkyne position, the influence of benzo-fusion and hetarene fusion, as well as the changes induced by heteroatoms in the enediyne skeleton, are within the scope of this review. With the exception of more complex heterocyclic hetarene-fused enediynes the experimental data of electronic substituent effects on the thermal Bergman cyclisation of enediynes follow theoretical predictions. A review with 57 references.

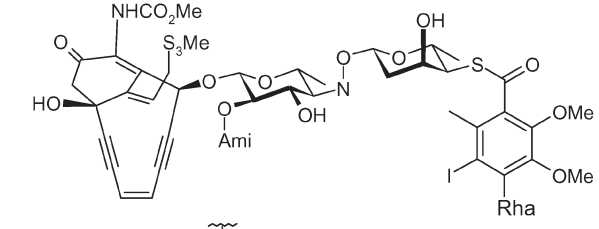
Keywords: Enediynes; Bergman cyclisations; Electronic substituent effects; Alkynes; DNA cleavage agents; Antibiotics; Cytotoxic compounds.

1. INTRODUCTION

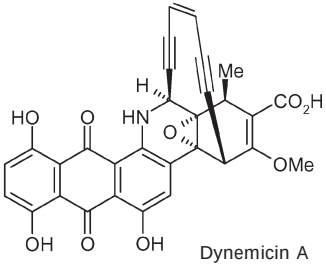
The naturally occurring antibiotics esperamicin A_1[1], calicheamicin γ_1^I[2] and dynemicin A[3] possess a cyclic enediyne structure. Through the attack of a nucleophile, the Bergman reaction is initiated, which leads to the formation of a benzenoid diradical. These diradicals abstract hydrogen atoms from DNA, which in turn is destroyed and leads to the death of the cell[4,5].



Esperamicin A_1



Calicheamicin γ_1^I



Dynemicin A

The principal reaction was studied by Bergman, who showed that the thermal cyclisation of (*Z*)-hexa-3-ene-1,5-diyne (**1**) leads to benzene-1,4-diyl (*p*-benzyne) (**2**), which forms benzene on hydrogen abstraction[6] (Fig. 1). The reaction to form the diradical is endergonic, and therefore occurs only at high temperatures ($t_{1/2}$ = 1 h at 155 °C)[7].

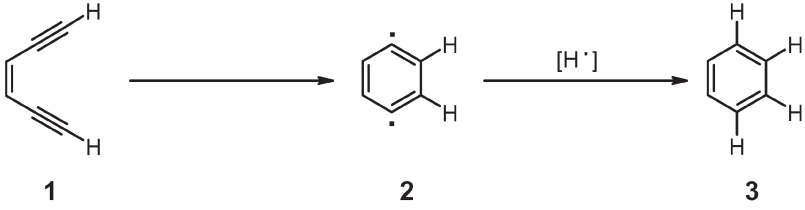


FIG. 1
Bergman cyclisation

In addition to the cyclisation to 1,4-didehydrobenzene (**2**), the possible cyclisation of enediynes to a fulvene diradical **4** was explored. Schreiner et al. showed in theoretical work[8] that due to lacking aromaticity or stabilisation through conjugation, the required reaction enthalpy of the cyclisation to **4** is very high (39.6 kcal/mol). Large groups at the terminal alkynyl positions should favor a reaction to **4**, but the sterically demanding groups could further increase the activation barrier[8]. As yet no fulvene derivatives via thermolysis of enediynes have been synthesised[9]. The corresponding reactions of ene-yne-allenes **6** are both known (Fig. 2). The Myers–Saito reaction leads to toluene diradical **7** in an exothermic reaction[10]. The so-called Schmittel cyclisation leads to the fulvene diradical **5**. Due to the lack of aromatic stabilisation the reaction is endothermic[11].

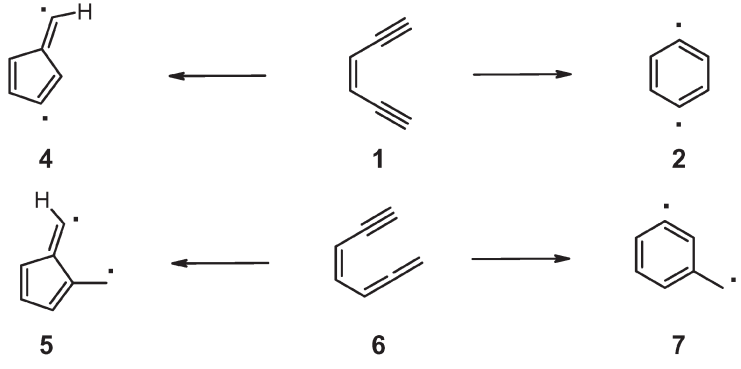


FIG. 2
Cyclisation pathways of enediynes and ene-yne-allenes

The effect of ring strain[12,13], metal ion co-ordination[14], and irradiation[15,16] on the cyclisation processes have been investigated and described, but substituents changing the electronic nature of the enediyne also alter cyclisation properties and cyclisation pathways. In this paper we review the reported examples of electronic substituent effects on the Bergman cyclisation and correlate them with theoretical predictions. As there are not many examples for electronic substituent effects on ene-yne-allene cyclisations known[17], we will focus on enediynes. Metal ion coordination may be regarded as substitution which changes the electronic properties of an enediyne significantly. A recent review by Basak[18] summarises examples of chelation-controlled Bergman cyclisations. However, in most cases it is difficult to separate the electronic from geometrical contributions to Bergman cyclisation in metalloenediynes[19]. The example given in Fig. 3 illustrates the situation[20]. The heterocyclic enediyne **8** undergoes thermal Bergman cyclisation upon heating to 170 °C. The C2···C7 distance, which has been used as an indicator for reactivity of cyclic enediynes, is 3.90 Å from X-ray structure analysis. Metal ion coordination with $CuCl_2$ or $ZnCl_2$ leads to a compression of the C2···C7 distance to 3.76 Å, but only the copper complex is more reactive. Differential scanning calorimetry measurements re-

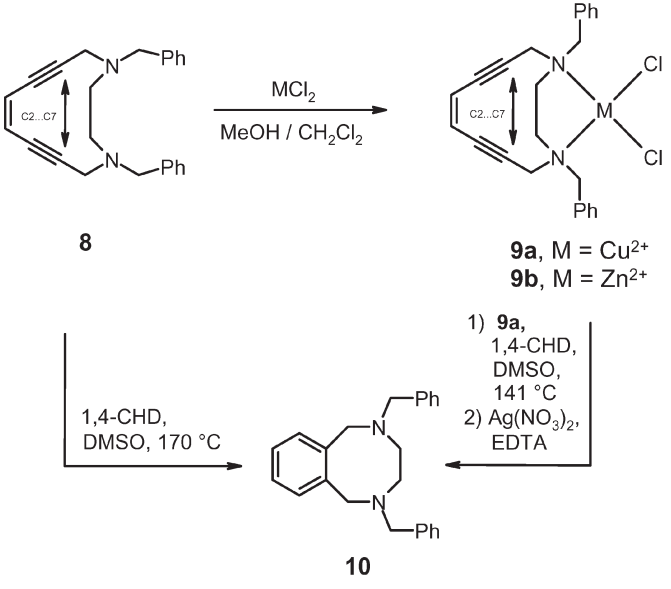


FIG. 3
Electronic and geometric contributions to Bergman cyclisation of metalloenediynes

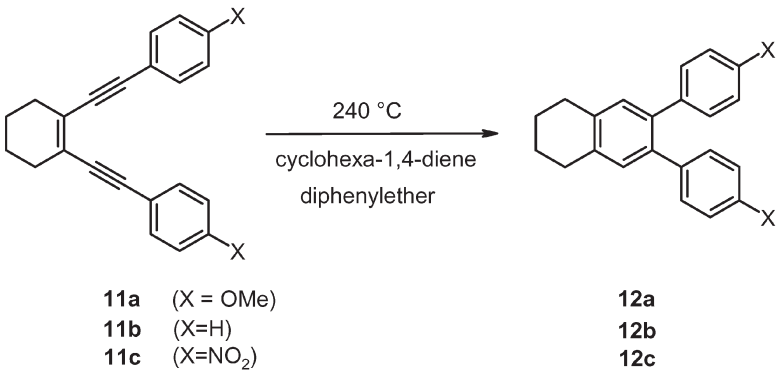
vealed reaction temperatures for the copper complex **9a** of 141°C, whereas the zinc complex **9b** becomes more stable with a reaction temperature of 207 °C. The authors explain the difference in reactivity by different electronic contributions of the ancillary chloride ligands. In the case of **9b** theoretical calculations suggest a significant through space contribution of the lone pair into the HOMO of the enediyne which lowers the reactivity. The geometrical contribution of zinc and copper ion chelation are comparable and the different electronic contributions become visible. This is exceptional and cannot be assumed in general. Therefore we will not cover the effect of metal ion chelation on the Bergman cyclisation in this review, although a significant, but usually not defined, electronic component is involved in many cases.

The effects of substituents in the vinylic and terminal alkyne position, the influence of benzo-fusion and hetarene fusion, as well as the changes induced by heteroatoms in the enediyne skeleton, are within the scope of this review and will be addressed.

2. SUBSTITUTION OF THE TERMINAL ALKYNE POSITION

Morokuma et al.[21] compared the enthalpies for the diradical formation from **1** and **6**. They calculated that the reaction of the ene-yne-allene **6** is exothermic and has smaller activation energy than the reaction of the enediyne system **1**. These results were confirmed experimentally[7,22]. In the case of the ene-yne-allene, a benzylic π-methylene radical is formed (see **7**), which is more stable than the benzene σ-radical (see **2**). In addition, the four-electron repulsion of two π-bonds of the alkynes in the same plane explains the larger activation energy required for enediyne cyclisation. In the case of the ene-yne-allene cyclisation, π-orbitals lie *anti* to the new formed C–C σ-bond and interact less. It was predicted that electron-withdrawing groups in the alkynyl position of an enediyne should reduce the electron density of the alkyne π-orbitals, and lower the repulsion and activation barrier of the reaction. This prediction was confirmed by Schmittel et al.[23] in the reaction of compound **11** (Fig. 4). Replacing the electron-donating methoxy substituents in **11a** by electron-accepting nitro substituents in **11c** leads to a decrease in the activation enthalpy of the cyclisation reaction. The activation entropy is thereby not significantly affected. It is presumed that the cycloaromatisation is accelerated by electronic stabilisation of the reaction intermediate.

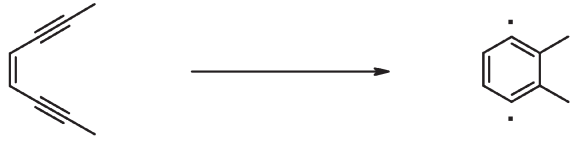
The transition state of the cyclisation is geometrically similar to the product, but electronically reminds more of the starting material. Schreiner



11a (X = OMe) **12a**
11b (X=H) **12b**
11c (X=NO_2) **12c**

FIG. 4
Substituted diaryl enediynes show different reactivity

et al. showed that the intermediate is "σ-aromatic" and therefore, substituents that influence the σ-framework of a molecule are the most effective in reducing the relative energies of the Bergman cyclisation[24] (Fig. 5). In a later publication of the same group, a different calculation method led to the result that cyclic electron delocalisation within the intermediate occurs perpendicular to the π-system[25].



13 **14**

FIG. 5
Bergman cyclisation of oct-4-ene-2,7-diyne (**13**)

The comparison of 1,4-benzyne (**2**) and 2,3-dimethyl-1,4-benzyne (**14**) shows that alkyl substituents at the alkynyl position have a large effect on the endothermicity of the Bergman cyclisation (ca. 12 kcal/mol). Alkyl substitution stabilises the enediyne alkynes and disfavors a cyclisation reaction. However, ring strain in cyclic enediynes can overcome this effect[26].

If this methyl group is functionalised with a hydroxy group in cyclic, benzo-fused systems, a small, yet significant activation of the reaction is observed experimentally. The parent system **16** has a half-life time ($t_{1/2}$) of 24 h at 84 °C, while the alcohol **15** decays with $t_{1/2}$ = 4.5 h at this temperature.

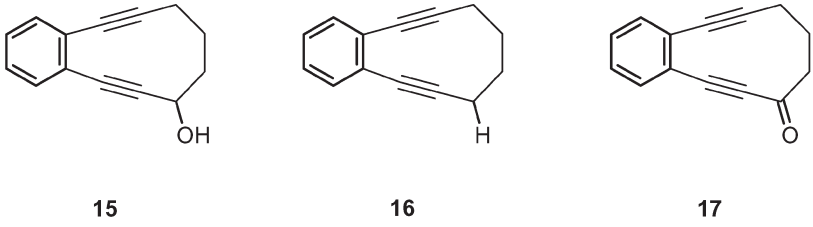


FIG. 6
Benzo-fused cyclic enediynes with propargylic substitution

The corresponding ketone **17** is far more reactive, with $t_{1/2} < 1$ h at the same temperature, but this can be accounted for by steric and electronic effects. In acyclic enediynes a carbonyl substitution did not significantly change the thermal reactivity. Calculations explain the observation of the predominant π-acceptor character of the carbonyl substituents, whereas σ-acceptor substituents are required for activation[27].

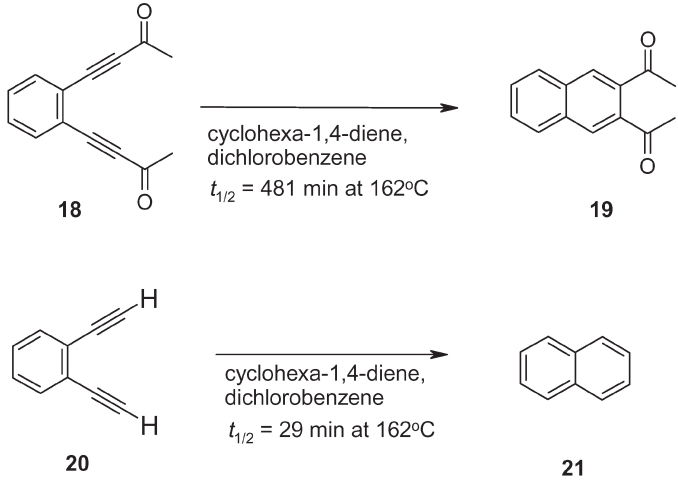
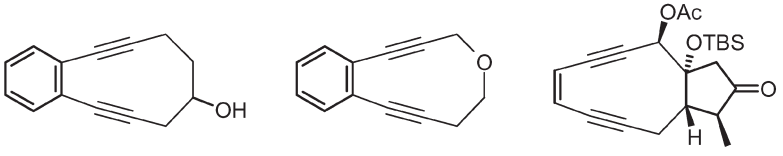


FIG. 7
Thermal cyclisation of a carbonyl substituted acyclic enediyne. The solvent dichlorobenzene consists of a mixture of regioisomers

Even when the hydroxy group is not in the α-position to the triple bond, but rather in β-position, activation is observed. The thermal reactivity is less than that of **15**, yet larger than of the unsubstituted parent system **16** (Fig. 6). When an oxygen is in propargylic position within the ring of an enediyne, such as in **23**, activation is also observable ($t_{1/2}$ = 52 h at 37 °C)[28]. In more complex systems, such as **24** with a half-life time of 13–14 h at

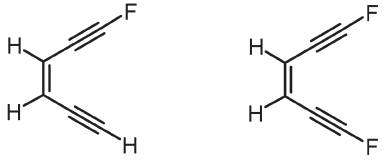
25 °C [29], the effect of the protected hydroxy groups on the reactivity cannot be well separated from other parameters, such as conformational constraints and ring strain.



22 **23** **24**

FIG. 8
Functionalised cyclic ten-membered enediynes

Computer-aided calculations have shown that the cyclisation of the parent system is strongly dependent on substituent effects. Strong σ-acceptors and/or π-donors lower the reaction barrier. Depending on the substituent, the HOMO of the cyclisation transition state is either of σ- or π-type. π-Donors lead to a decrease of the barrier through the stabilisation of the π-binding orbitals. σ-Acceptors favor the cyclisation by lowering the occupation of antibinding σ-orbitals. Examples of such substituents are: F, OH, NH_3^+ and OH_2^+ [30]. In the case of monofluoroenediyne **25a** and the difluoroenediyne **25b** (Fig. 9), the cyclisation to the diradical is predicted to be exergonic. So far fluoro-substituted enediynes have not been synthesised, but their photochemical generation within a matrix in neon at 3 K was reported (Fig. 10). In the photochemical generation of tetrafluoro-1,4-benzyne (**29**) from 1,2,4,5-tetrafluoro-3,6-diiodobenzene (**26**), the fourfold substituted enediyne **28** was observed as a side product[31].



25a **25b**

FIG. 9
Mono- and difluoroenediynes

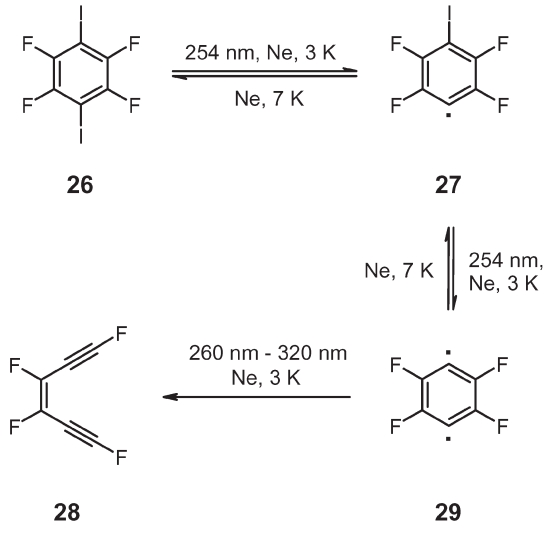


FIG. 10
Photochemical generation of tetrafluoroenediyne **28** in a neon matrix

Another example of the ability of electron-withdrawing functionalities at the alkyne termini to decrease the activation barrier to the Bergman product has been reported by Zaleski recently[32]. Bis(bromoethynyl)tetraphenylporphyrin **30** cyclises to the corresponding cycloaromatised Bergman product **31** under oxidative conditions at room temperature (Fig. 11). The analogous bis(iodoethynyl)tetraphenylporphyrin is stable under these conditions.

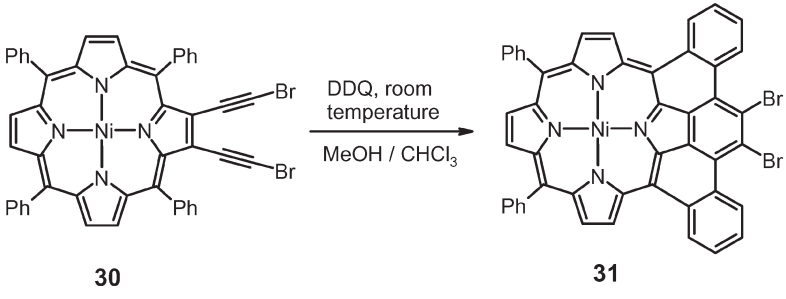


FIG. 11
Ambient temperature activation of haloporphyrinic enediynes

The clean and facile thermal cyclisation of halogenated enediynes has been used for the preparation of 2,3-dibromoarene, which are otherwise difficult accessible[33]. Bis(bromoethynyl)arenediynes are prepared by the desilylative halogenation of the corresponding trimethylsilyl derivatives. Clean cycloaromatisation is achieved by simple heating of dilute solutions of the halogenated compound **32** in benzene/cyclohexadiene mixtures (Fig. 12). A single recrystallisation of the crude product from heptane provided pure 2,3-dibromonaphthalene **33** in 70% yield. The efficiency with which **32** undergoes cycloaromatisation is unusual for an acyclic enediyne and might be explained by the electron-withdrawing effects of the halogens.

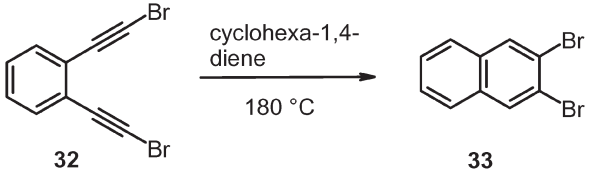


FIG. 12
Cycloaromatisation of halogenated enediynes

The predicted effect of a nitrogen atom as acetylene substituent of the enediyne was explored with sulfonamidoenediynes **34** (Fig. 13). The structures are stable and crystalline due to strong electron-acceptor properties of the sulfonyl group[34]. The required σ-acceptor effect of the nitrogen atom on the enediyne system remains, while the π-donating character of the nitrogen atom is reduced similar to an ammonium ion. Compound **34** cyclises thermally to the Bergman product **35**. The kinetic reveals some activation compared with the unsubstituted system[35]. However, comparison is difficult in this case, because of changing steric requirements.

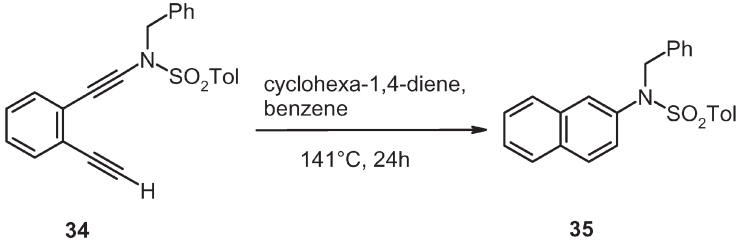
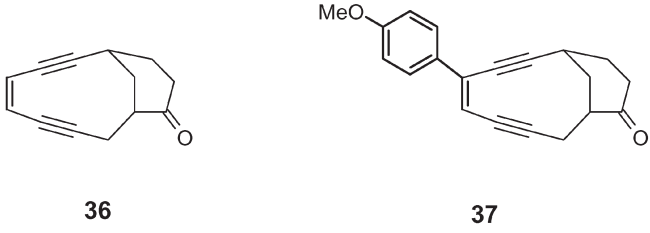


FIG. 13
Thermal cyclisation of an enediyne sulfonamide

3. SUBSTITUTION OF THE VINYL POSITION

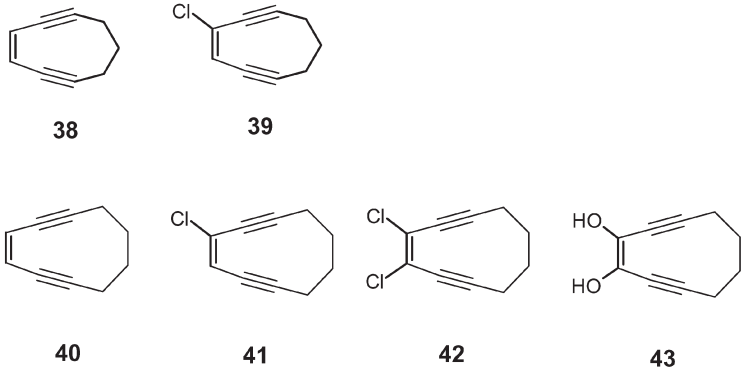
The bicyclic enediyne **36** is highly reactive and cyclises spontaneously at room temperature. By introducing a 4-methoxyphenyl substituent in the vinyl position (Fig. 14), the enediyne **37** is stabilised. Upon heating to 80 °C this compound cyclises. The authors suggest that the 4-methoxyphenyl substituent stabilises the ground state more than the reaction intermediate, disfavoring the reaction. In addition, the electron-donating aryl substituent may increase the four-electron repulsion in the transition state, as described in other cases by Morokuma et al.[36]



36 **37**

FIG. 14
Substitutent effect in bicyclic enediynes

Thereupon other substituents in the vinyl position were investigated. Chlorine influences cyclisation of cyclic enediynes (Fig. 15): its rate is significantly reduced. Thus the nine-membered enediyne **38** is extremely labile, so that its half-life time cannot be measured. The chlorinated analogue **39** can be isolated and having a half-life time of 8 h at 0 °C. The same is found for the ten-membered series: the rate of cyclisation is slower for enediyne



38 **39** **40** **41** **42** **43**

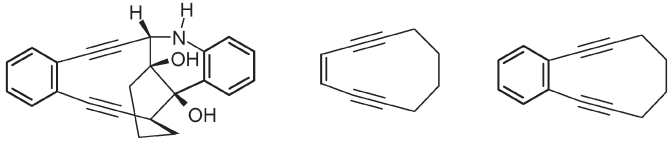
FIG. 15
Cyclic chlorinated enediynes and the unchlorinated parent system

41 compared with the unsubstituted **40**, and the addition of a second chlorine, such as in **42**, significantly retards the reaction rate further. Enediyne **41** has a half-life time of 18 h at 50 °C, while enediyne **42** cyclises with a half-life time of 24 h at 170 °C [37].

Computational work using DFT methods can help explain the effects in these molecules. The observed decrease in cyclisation rate is based on the enhanced cyclisation barrier. Further investigations showed that σ-electron-withdrawing groups in the vinylic position generally inhibit the Bergman cyclisation, while σ-electron-donating groups in these positions reduce the barrier. The effect of π-conjugation is small. The stabilising effect of halogens is explained by a destabilising interaction between an in-plain halogen lone pair and an occupied in-plane acetylenic orbital[38]. Theory predicts similar effects for different halogen atoms and an additive inhibitory effect of a second halogen on cyclisation. The reactivity of dihydroxyenediyne **43** is similar to that of dihalo structures[39].

4. BENZO-FUSION

Another form of "vinyl substitution" is benzo-fusion. Benzo-fusion in the ene position of the dynemicin analogue **44** (Fig. 16) increases the cyclisation barrier in comparison to non-fused systems[40]. A simple model system shows that the benzo-fusion of cyclodecenediynes leads to an increase in the cyclisation barrier. Structure **16** is stable over many weeks at room temperature, while the non-benzo-fused analogue **45** has a half-life time of 18 h at 37 °C.



44 **45** **16**

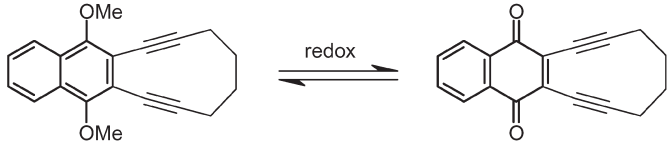
FIG. 16
Benzo-fused cyclic enediynes

Cyclic enediynes **46** and **47** follow the same pattern. They only differ from the above example by replacement of the methylene group with a sulfonamide unit. Enediyne **46** has a half-life time of 72 h at 23 °C and is thus considerably more reactive than its benzo-fused analogue **47** ($t_{1/2}$ = 52 h at 65 °C)[41,42].

46 **47**

FIG. 17
Ten-membered, nitrogen containing cyclic enediynes

The reactivity of 1,4-dimethoxynaphthalene derivative **48** and 1,4-naphthoquinone **49** was compared (Fig. 18). Consistent with a simple picture relating the extent of double bond character in the ene part to the enediyne with the rate of arene-1,4-diyl formation, the hydroquinone derivative is much less reactive ($t_{1/2}$ > 7 days at 120 °C) compared with the corresponding quinone ($t_{1/2}$ > 88 h at 40 °C)[43].



48 **49**

FIG. 18
Reactivity change by redox reaction: naphthohydroquinone derivative **48** and more reactive naphthoquinone enediyne **49**

Acyclic enediynes behave differently. Experimental values for the activation parameters could be determined for the cyclisation of the parent system **1** and its benzo-fused analogue **50** to the corresponding dihydroaromatics **2** and **51**, respectively (Fig. 19). The activation barrier for the cyclisation as well as for the reverse ring opening is lower for the benzo-fused case[6,44].

The cyclisation of the benzo-fused system is more endothermic, which is explained by smaller gain in aromatic resonance stabilisation energy upon naphthalene formation compared with the benzene formation. These effects were confirmed by ab initio studies[45].

The cyclisation of benzo-fused enediynes is influenced by substituents in the *para* position on the benzene ring. Electron-withdrawing groups such in 1,2-diethynyl-4-nitro-benzene (**52**) (Fig. 20), increase the reactivity in comparison with the parent system **50**, while electron-donating groups such as those in **53**, decrease the reactivity. These effects, however, are quite small[46].

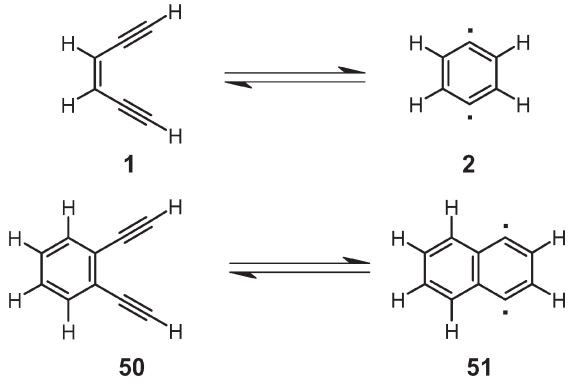


FIG. 19
Benzo-fused **50** and non-fused cyclic enediyne **1** and their Bergman cyclisation products **51** and **2**

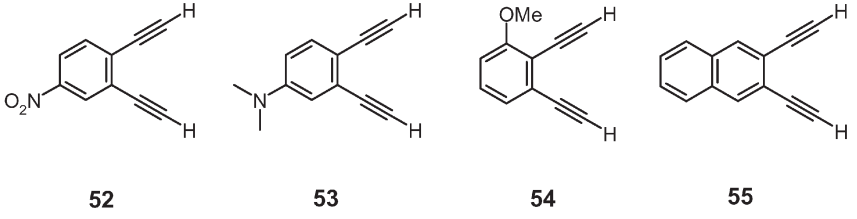


FIG. 20
Substituted 1,2-diethynylbenzenes

Theoretical investigations predicted that electron-withdrawing groups in the *ortho* position have a greater influence on the cyclisation than substituents in the *para* position[34]. 2,3-Diethynyl-1-methoxybenzene (**54**) shows, contrary to these calculations, that methoxy groups, although they are electron-donating groups in the *ortho* position, have an accelerating effect. However, no rationale is provided for this *ortho*-methoxy group effect[47].

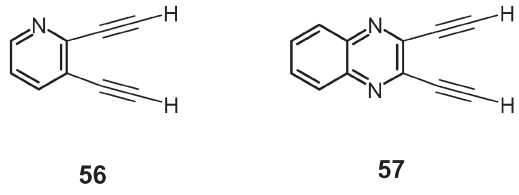
Theoretical examinations of the aromaticity of the Bergman reaction came to the conclusion that benzo-fusion considerably influences the endothermicity of the cyclisation, while the influence on the reaction barrier is small[25]. Furthermore, it could be shown that the benzo-fusion can influence which step of the Bergman reaction becomes rate-determining. The cyclisation step leading to the diradical can be rate-determining, so that the rate of the whole reaction is independent of the concentration of the hydrogen donor. In contrast, the hydrogen abstraction may be rate-determining, making the overall reaction rate-dependent on the concentra-

tion of the hydrogen donor. The kinetic data of the parent system **1** show that the conversion of the enediyne is independent of the concentration of the quencher, and the rearrangement to the benzene-1,4-diyl (**2**) is the rate-determining step. For **50** and **55**, kinetic data reveal a rate dependence on the hydrogen donor concentration, which indicates that the hydrogen abstraction step is rate-determining. The effect is also observed in cyclic enediynes. The reaction rate of benzo-fused enediyne **16** shows a dependence on the concentration of the hydrogen donor, while **45** does not. Two rationales are provided to explain the effects. In benzo-fused enediynes the back reaction of the diradical to the enediyne is faster than the quenching reaction, as only a part of the aromatic resonance energy is lost during the back reaction of the diradical from **16**, whereas in the case of **45** the whole resonance energy is lost. Another explanation is based on the assumption that the benzo-fusion induces a considerable splitting of the singlet–triplet energy of the diradical, which could lead to a reduction in the rate of hydrogen abstraction in the singlet ground state[48]. A theoretical study supports that the first mechanism – namely an increase in the rate of the retro-Bergman cyclisation – causes the change of the rate-determining step[49].

5. HETEROARENE FUSIONS

Theoretical calculations show that the structures **56**–**59** (Fig. 21) almost have the same cyclisation barrier, and lie only slightly below that of the unsubstituted benzo-fused enediyne **50**. Heteroatom substitution in the benzene ring of the enediyne system seems to have only a slight influence on the cyclisation[50]. However, the experimental data for the compounds show an inconsistent picture. The pyridine **56**, with an activation energy of E_a = 21.5 kcal/mol, is considerably more reactive than **52** (E_a = 25.1 kcal/mol), quinoxaline **59** is less reactive (E_a = 33.6 kcal/mol)[51]. Structure **59** also shows an effect which depends on the polarity of the solvent. The half-life time of structure **59** at 168 °C in THF is 16 min while in acetonitrile the half-life time increases to 361 min [52].

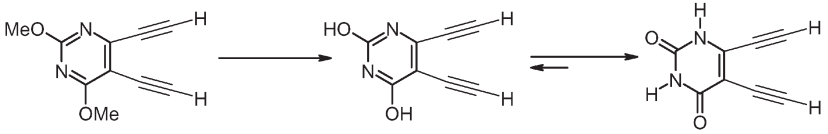
An exceptional rapid cyclisation was found for the pyrimidine **60** (Fig. 22). So far no explanation has been provided for the observation. Cleavage of the methoxy groups in **60** leads to lactim **61**, which can tautomerise to the even more reactive lactam **62**. Notably the activation energy of **60** is smaller than that of **62**, providing no rationale for higher reactivity. As explanation, in addition to the benzo-fusion effect, the lower ground state energy of **62** in comparison with **60**, is used, so that at the same temperature more molecules are able to react[53].



56 **57**

58 **59**

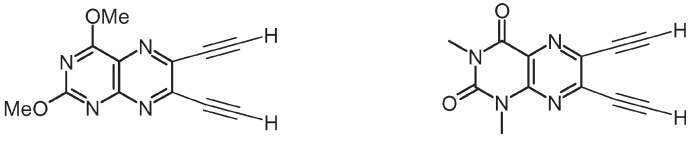
FIG. 21
Heteroarene-fused enediynes



60 **61** **62**

FIG. 22
Reactive hetarene-fused enediynes

A similar result is observed with the lumazine derivatives **63** and **64** (Fig. 23). Structure **63** ($t_{1/2}$ = 6.1 min at 165 °C, 100 equivalents of cyclohexa-1,4-diene) cyclises more slowly than **64** ($t_{1/2}$ = 10.1 min at 165 °C, 100 equivalents of cyclohexa-1,4-diene) to the corresponding Bergman product. Interestingly, the non-*N*-methylated analogue of **64** does not form a Bergman product under the reaction conditions[54].

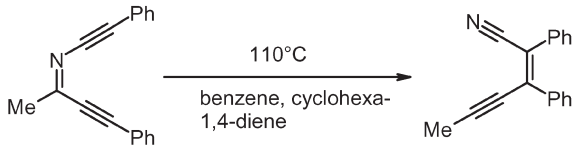


63 **64**

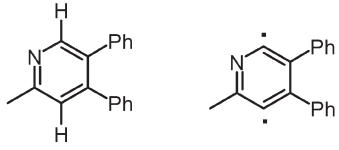
FIG. 23
Lumazine derivatives

6. HETEROENEDIYNES

The *C,N*-dialkynylimine **65** (Fig. 24), which is also referred to as azaenediyne, isomerises upon heating to the corresponding nitrile **66**.



65 **66**



67 **68**

FIG. 24
Thermolysis of azaenediyne **65**

In the first experiments the expected Bergman product, pyridine **67**, could not be isolated. The ring opening in this case is faster than the quenching reaction. Thus no direct comparison with cyclisations of enediynes could be made. Therefore the rates of the isomerisation were compared. The isomerisation of imine **65** proceeds much more rapidly than the isomerisation of the corresponding hexenediynes[55], but under conditions where didehydropyridine **68** intermediate is protonated, a hydrogenated product was isolated. Compound **67**, together with nitrile **66**, was isolated in small amounts on the addition of acid[56]. Calculations show that protonation of **68** increases not only the singlet–triplet distance, which is now similar to that of **2**, but also the barrier. Protonation thus partially cancels the interference caused by the heteroatom[57].

7. CONCLUSION

We have summarised reports of electronic effects on the cyclisation of enediynes. Substitution of the terminal alkyne and the vinylic position, benzo-fusion, hetarene fusion, and azaenediynes were examined.

Substitutions in the terminal alkyne position generally affect enediyne cyclisation more than substitutions in the vinylic positions. Theoretical

predictions are well confirmed by experimental data, which show an increase in enediyne thermal reactivity due to alkyne π- or σ-acceptor substituents. Theoretical predictions made for the vinylic substitutions also correspond well with the experimental data. Electron-withdrawing groups in vinylic positions stabilise the enediynes and make them less reactive. σ-Donor substituents slightly decrease the cyclisation barrier, while π-conjugation shows only little influence.

The effect of benzo-fusion on the thermal reactivity of enediynes is inconsistent. While benzo-fused acyclic enediynes are activated for cyclisation, in cyclic enediynes the reaction is disfavored. Substitution of the fused benzene ring influences reactivity only slightly. Electron-withdrawing substituents increase, while electron-donating substituents decrease the reactivity. The benzo-fusion determines whether the cyclisation or hydrogenation of the diradical becomes the rate-limiting step of the thermal Bergman reaction.

Hetarene fusions show no consistent effects. So far, the theoretical predictions do not correspond with the experimental results. Theory predicts similar activation energies for thermal cyclisation of different nitrogen-containing heteroatoms, while the experimental data reveal significant differences.

Introducing a nitrogen atom into the enediyne system accelerates its isomerisation to the corresponding nitrile. A hydrogenated Bergman cyclisation product could only be isolated if the nitrogen of the azaenediyne is protonated. Experimental results for this process correspond well with theoretical investigations.

In conclusion, electronic substituent effects on the thermal Bergman cyclisation of enediynes are well documented by experimental data and explained by theoretical work. Only more complex heterocyclic systems show poor correlation. With this level of knowledge and understanding, electronic substituent effects can now be used for designing enediynes with defined and switchable thermal reactivity.

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