The Bergman reaction of dynemicin A – a quantum chemical investigation

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Abstract

For the first time, the Bergman reaction of a naturally occurring enediyne, namely dynemicin A, is fully investigated at the DFT level of theory using the B3LYP hybrid functional and VDZ basis sets. The calculated geometry of dynemicin A agrees well with the X-ray structure of deoxydynemicin A. The activation barrier is calculated to be 19.4 kcal/mol, while the reaction energy is exothermic by −2.1 kcal/mol, reflecting the destabilization of the enediyne unit by incorporation into a tricyclic ring system. The energetics of dynemicin A reveal that the enediyne is biologically active at body temperature. © 2002 Elsevier Science B.V. All rights reserved.

1. Introduction

The astonishing biological activity of the naturally occurring enediynes has led to increased efforts of using enediynes as anticancerogenes by exploiting their ability to destroy the DNA of tumor cells [1]. Dynemicin A (**1**, see Scheme 1), an enediyne antibiotic isolated from *Micromonospora chersina* sp.nov.N956-1, has been the subject of intensive chemical and biological research due to its broad spectrum of antibacterial and anticancer activities [2,3]. Enediyne **1** is highly potent, having minimal inhibitory concentrations and shows high activity when tested in vivo [1,4].

In general, the enediyne antibiotics have first to dock to the minor groove of DNA and then they have to be activated (*triggered*) before their reaction with DNA [1]. Enediyne **1** is triggered mainly via reduction by NADPH, thiols, other reducing agents or visible light [1,5]. One- or two-electron transfer to **1** leads to hydroquinone (see Scheme 1). The hydroquinone further rearranges via opening of the epoxide ring to a quinone methide and, then, by protonation a quinone alcohol (**2**, Scheme 1) is formed, which is the starting point for a Bergman cyclization reaction [5]. The Bergman cyclization reaction [6] generates a didehydrobenzene biradical **3** in its singlet state, which abstracts hydrogens from the DNA double strands resulting in its cleavage and, by this, causes cell death (Scheme 1) [1].

Quantum chemical investigations have played an important role to support experimental research on enediynes and to aid the understanding of their high biological activity. However, the quantum chemical studies focused so far on the

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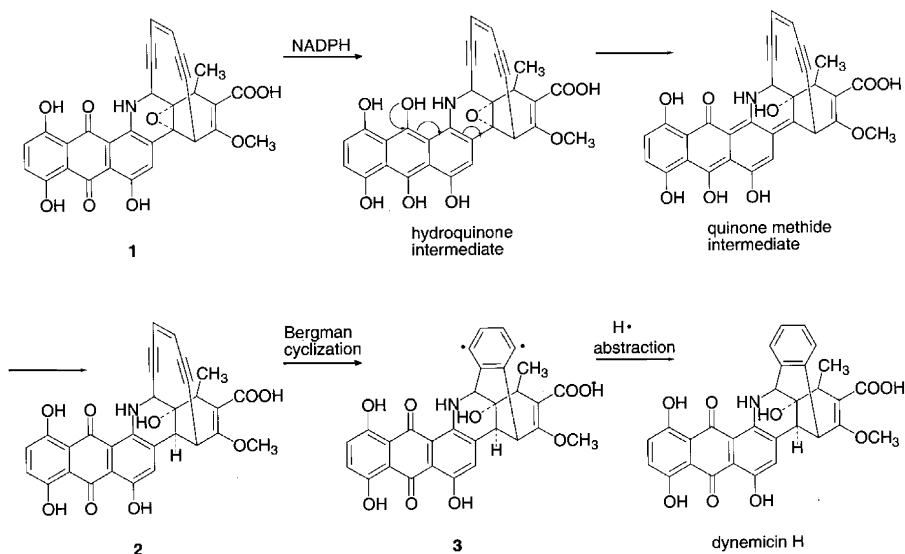
Scheme 1.

Bergman reaction of small model enediynes while naturally occurring enediynes were, because of their size, considered too difficult to be calculated at the ab initio level. In this work, the activation reaction of a naturally occurring enediyne is studied for the first time exclusively by density functional theory (DFT) [7,8]. The work presented is part of a larger project that involves the study of the Bergman reaction of various naturally occurring enediynes, secondly an elucidation of the triggering mechanism leading to the Bergman cyclization reaction, and finally aims at developing nontoxic enediyne anticancer drugs.

In this work, the energetics of the Bergman reaction of **2** is investigated and related to the biological activity of the compound. In particular, the question how the multicyclic framework of **2** is influencing the activation energy will be considered.

2. Computational methods

A quantum mechanical description of the Bergman cyclization reaction of **2** leading via **TS(2–3)** to biradical **3** requires the calculation of molecules with 61 atoms. This leads to more than

640 basis functions when an augmented valence double zeta basis set is used. Calculations with such a large number of basis functions are feasible at the DFT level [7,8], however, for a complete DFT geometry optimization they still imply a heavy computational load. Therefore, we use in this work Pople's 3-21G split-valence basis set [9] for the geometry optimization because this decreases the number of basis functions to just above 400. Single-point calculations at DFT/3-21G geometries employing the 6-31G(d) basis set [10] are carried out to verify the 3-21G results.

So far no DFT/3-21G calculations on enediynes have been reported since according to the standards of wave functions theories (WFT) this basis set is too small to lead to reasonable results, in particular if electron correlation has to be considered. However, DFT is less sensitive to the size of the basis set and therefore it is reasonable to test even such a small VDZ basis set for its usefulness when describing reaction mechanism. We will demonstrate in this work that DFT calculations with the 3-21G basis set lead to surprisingly reliable description of the Bergman reaction of an enediyne.

The B3LYP hybrid functional [11–13] was used at the restricted DFT (RDFT), unrestricted DFT

(UDFT), and broken-symmetry-UDFT (BS-UDFT) levels of theory. RDFT/B3LYP calculations were carried out for the singlet states, however, in each case the internal and external stability of the RDFT solution was tested. If the latter was not fulfilled as in the case of the singlet biradicals, a BS-UDFT calculation was performed for the singlet state. BS-UDFT is known to provide a useful description of the singlet biradical generated in the Bergman cyclization reaction [14–16]. The triplet states investigated in this work were calculated at the UDFT level of theory. For the calculations, the program packages COLOGNE 2001 [17] and GAUSSIAN 98 [18] were used.

3. Results and discussion

For reasons of comparison, B3LYP/3-21G geometry optimizations and B3LYP/6-31G(d)//B3LYP/3-21G single point calculations were carried out for two reference systems: (a) (*Z*)-hexa-1,5-diyne-3-ene (**4**) rearranging to the singlet biradical *p*-didehydrobenzene (**5S**); (b) cyclodeca-1,5-diyne-3-ene (**6**) rearranging to the cyclohexane-annelated *p*-didehydrobenzene singlet biradical (**7S**). Since accurate experimental [19] and theoretical data [14,16,20,21] are available for the energetics of the parent system **4**–**5S** it is a useful reference for the evaluation of the reliability of

B3LYP/3-21G descriptions. The system **6**–**7S** is then a suitable link between the acyclic reference system **4**–**5S** and the tricyclic target system **2**–**3S**.

B3LYP/3-21G geometries of the molecules involved in the Bergman reaction of dynemicin A are shown in Fig. 1 (**2**), Fig. 2 (**TS(2–3)**), and in Fig. 3 (**3S**). The energetics determined for the Bergman reaction of the two reference and the target system is given in graphical form in Fig. 4. The numbering of the C atoms in the enediyne units is adjusted to that used for **2** to facilitate the comparison between the target and the reference systems.

The B3LYP/3-21G geometries of **4**, **TS(4–5)**, and **5S** closely resemble the corresponding B3LYP/6-31G(d) geometries differing by less than 0.05 Å and 0.5°. The largest deviations are found for the through-space distance C2C7 in enediyne **4** (3-21G: 4.432; 6-31G(d): 4.478 Å) and transition state **TS(4–5)** (3-21G: 1.927; 6-31G(d): 1.978 Å), which reflect the fact that the density tails with the polarized basis are longer thus leading to larger exchange repulsion (steric repulsion) between the in-plane π-electrons of the triple bonds. The latter interactions do not only play a role with regard to the relative stability of the enediyne but also when the new C2–C7 bond is formed: The in-plane π–π interactions determine the magnitude of the barrier for the electrocyclic ring closure [22].

The measured activation enthalpy of the Bergman reaction of **4** is 28.9 kcal/mol at 400 K [19],
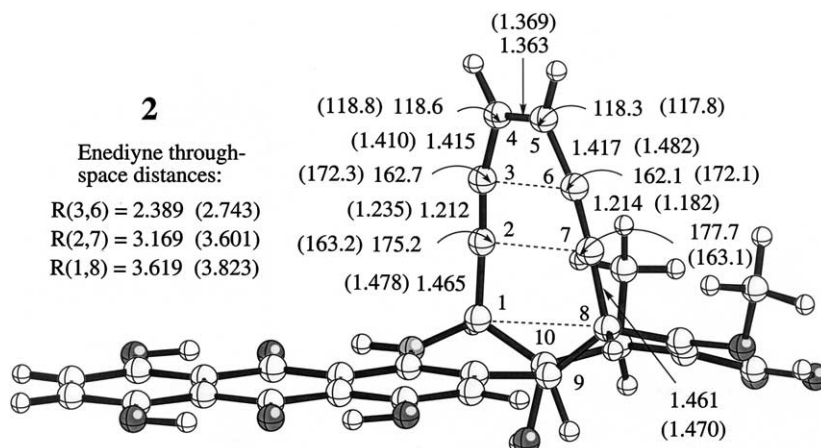

Fig. 1. B3LYP/3-21G geometry of the alcohol **2** of dynemicin A. Data from X-ray diffraction analysis of deoxydynemicin A as determined in [23,24] are given in parentheses. Bond lengths in Å, angles in degrees.
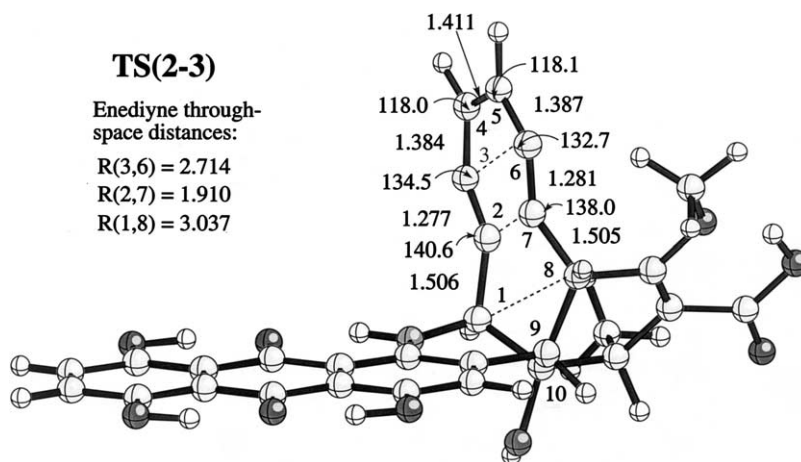
Fig. 2. B3LYP/3-21G geometry of the transition state **TS(2–3)** of the Bergman reaction of dynemicin A. Bond lengths in Å, angles in degrees.
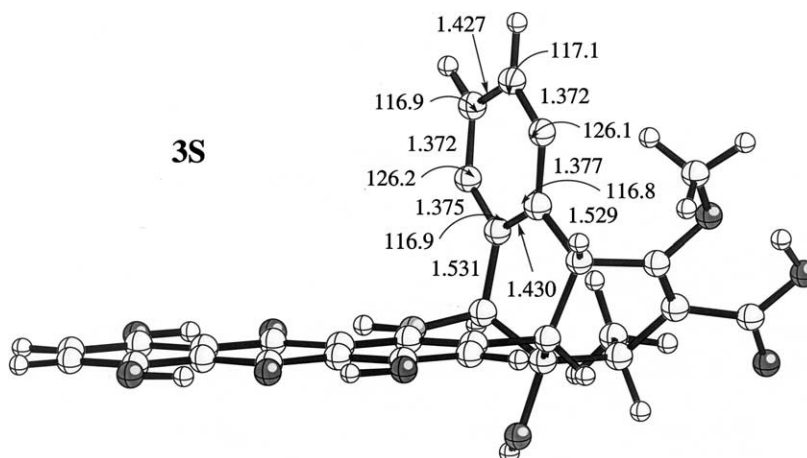

Fig. 3. B3LYP/3-21G geometry of the singlet biradical of the Bergman reaction of dynemicin A (**3S**). Bond lengths in Å, angles in degrees.

which corresponds to an energy barrier of 30.1 kcal/mol at 0 K (without any zero-point energy corrections) [14]. The corresponding values for the reaction energy at 0 K and the energy barrier for the retro-Bergman reaction are 7.8 and 22.3 kcal/mol, respectively (see Fig. 4) [14]. Both B3LYP/3-21G and B3LYP/6-31G(d) reproduce the barrier for the Bergman reaction accurately (30.8 and 30.9 kcal/mol, see Fig. 4). However, B3LYP/3-21G gives also reliable values for the reaction energy (7.7 kcal/mol) and the barrier for retro-Bergman

reaction (23.1 kcal/mol) while B3LYP/6-31G(d) underestimates the former value (2.9 kcal/mol) and overestimates the latter value (28.0 kcal/mol, Fig. 4). This is due to the fact that the 6-31G(d) basis leads to a seemingly better description of biradical **5S** (without accomplishing a similar improvement for **4** and **TS(4–5)**, see above) thus lowering its energy relatively to enediyne **4** and **TS(4–5)**. For the singlet–triplet (S–T) splitting, the B3LYP/3-21G value of 3.2 kcal/mol is again closer to the experimentally based energy splitting of 3.5 kcal/
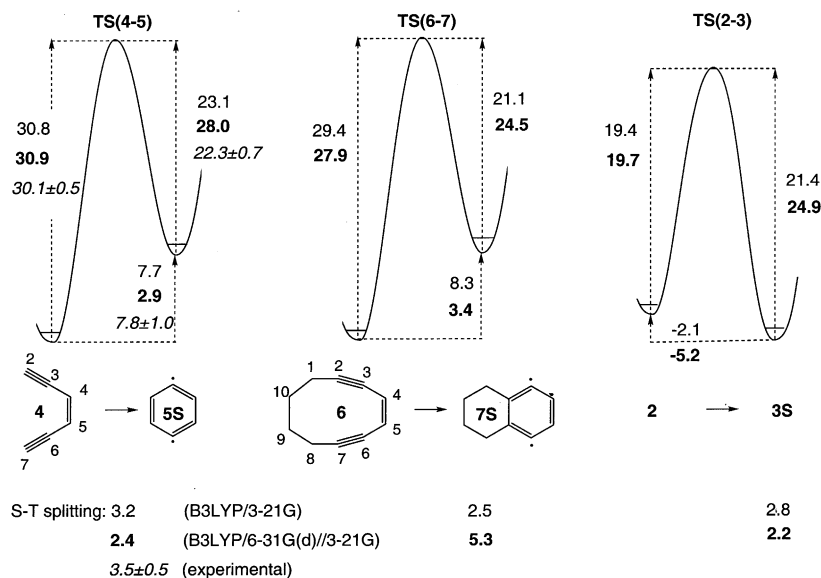
Fig. 4. Calculated energy profiles for the Bergman reactions of systems **2**, **4**, and **6**. Values are given in kcal/mol. The experimental values are obtained from [19] and corrected to energies at 0 K according to [14]. Note that the numbering of atoms follows that chosen for **2** (see Fig. 1).

mol [16] than the B3LYP/6-31G(d) value of 2.4 kcal/mol (Fig. 4).

The same observations with regard to calculated geometries and the energetics of the Bergman reaction are made in the case of the reaction system **6–7S**. The activation energies (at 0 K without zero-point energy corrections) are similar for the two basis sets (3-21G: 29.4; 6-31G(d): 27.9 kcal/mol, Fig. 4) while reaction energy, energy barrier for the retro-Bergman reaction, and the S–T splitting differ by 3–5 kcal (Fig. 4) where the more likely values are predicted by the 3-21G basis set.

We conclude that B3LYP with the 3-21G basis set provides the most reliable description of the Bergman reaction of the parent system **4–5S** ever published (deviations smaller than 1 kcal/mol from experimental values). Also the values for the system **6–7S** are reasonable. This of course may be due to a fortuitous cancellation of errors, nevertheless the 3-21G basis becomes in this way an excellent tool to investigate the naturally occurring enediynes such as **1** for which calculations with larger basis sets are very time consuming or impossible.

The crystal structure of deoxydynemicin A was determined by various authors [23,24]. The calculated geometry of **2** (see Fig. 1) can not directly be compared with the X-ray diffraction data because the former molecules possesses an epoxide ring, which has a strong influence on the enediyne unit and in addition has one of the OH groups in the anthraquinone part oxidized to a carbonyl group. The geometrical changes due to the opening of the epoxide ring in the course of the reaction $1 \rightarrow 2$ (Scheme 1) are crucial. Although the overall shape of deoxydynemicin A and the calculated structure of **2** are similar, the enediyne unit is asymmetrically distorted in the crystal structure of deoxydynemicin A (see difference in the triple bond lengths, Fig. 1). The through-space distances $R(3,6)$, $R(2,7)$, and $R(1,8)$ of the latter structure are 0.2–0.4 Å longer than those of the calculated geometry.

In **TS(2–3)** (see Fig. 2), the enediyne unit is distorted by reducing distance $R(2,7)$ to 1.910 Å, which leads to a lengthening of the triple bonds to 1.277 and 1.281 Å, respectively. The geometry of the rest of the molecule changes surprisingly little,

which simply means that the global shape of the molecule is retained during the Bergman reaction. Once the molecule has docked into the minor grove of DNA, the Bergman reaction does not change the docking situation. This is also reflected by the calculated geometry of biradical **3S** (Fig. 3). Although the changes in the enediyne part are substantial caused by the newly formed C2C7 bond (1.430 Å) and the aromatization of ring C2C3C4C5C6C7, the delivery system (isoquinone and anthraquinone parts) possess still the same geometry.

At the B3LYP/3-21G level of theory, an energy barrier of 19.4 kcal/mol is obtained for the Bergman reaction of **2** differing only slightly from the corresponding B3LYP/6-31G(d) value of 19.7 kcal/mol. The reaction is calculated to be exothermic by −2.1 kcal/mol leading to a retro-Bergman barrier of 21.4 kcal/mol (Fig. 4). As observed for the reference systems, the corresponding 6-31G(d) values deviate by 3–4 kcal/mol due to a typical underestimation of the B3LYP/6-31G(d) level of theory.

Utilizing entropy changes and temperature corrections obtained for the system **6–7S**, the reaction rate constant of **2** at room temperature is estimated to be $k = 1.8 \times 10^{-3}$ s^{-1}, which is sufficiently fast to guarantee a high biological activity of **2** at body temperature.

It has been argued [20] that by introducing steric strain into the enediyne system, which is less felt by the transition state than by the reactant, a lowering of the energy barrier can be achieved. This argument seems to be confirmed by the lowering of the energy barrier from about 31 kcal/mol (**4**) to 19 kcal/mol (**2**) when the enediyne unit is introduced into a tricyclic ring system where the enediyne ring is bridging an iso-quinone unit (see Scheme 1). This can be further illustrated using the through-space distances between the interacting centers as they are calculated for enediynes **4**, **6**, and **2** (see Table 1).

The reduction of the distance $R(2,7)$ from the equilibrium value of the enediyne to the the value valid for the transition state is 2.504 Å for **4** (from 4.432 to 1.928 Å, Table 1), 1.546 Å for **6** (from 3.407 to 1.861 Å), and just 1.259 Å **2** (from 3.169 to 1.910 Å), i.e., in the latter case the distance shortening needed for establishing a new C2C7 bond in the transition state of the Bergman reaction is already induced by the ring framework of **2**. In the transition state, calculated distances $R(2,7)$ are comparable (1.928, 1.861, 1.910 Å, Table 1) although a slight tendency for shorter values is observed for the cyclic systems. The squeezing of the 2,7-distance in **2** is supported by a relatively short 1,8 distance ($R(1,8) = 3.619$ Å compared to 3.784 Å in **6**, see Table 1) where the latter is enforced by the tricyclic ring system. The distance parameters verify that the strain in the enediyne unit of **2** is enlarged (stronger exchange repulsion between the in-plane π-electrons) thus destabilizing the reactant and lowering in this way the reaction barrier to 19.4 kcal/mol.

The S–T splitting of **3S** (2.8 kcal/mol, Fig. 4) is slightly smaller than for the parent biradical **5S** (3.2 kcal/mol; exp.: 3.5 kcal/mol [16]). This indicates a slight increase in the biradical character

Table 1

Calculated through space distances for three enediyne systems[a]

		4/TS(4–5)	6/TS(6–7)	2/TS(2–3)
A Enediyne	$R(3,6)$	2.977	2.759	2.389
	$R(2,7)$	4.432	3.407	3.169
	$R(1,8)$	–	3.784	3.619
B Transition state	$R(3,6)$	2.729	2.712	2.714
	$R(2,7)$	1.928	1.861	1.910
	$R(1,8)$	–	3.111	3.037
$\Delta R(\text{B} - \text{A})$	$R(3,6)$	0.248	0.047	0.325
	$R(2,7)$	2.504	1.546	1.259
	$R(1,8)$	–	0.673	0.582

[a] Distances in Å. All calculations at the B3LYP/3-21G level of theory. For ring numbering, see Figs. 1 and 4.

and hence increased H-abstraction ability from DNA. We conclude that **1** if properly triggered rapidly undergoes Bergman cyclization at body temperature. The biradical generated will abstract H atoms from DNA thus causing cell death.

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