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On the Distribution of Linear *vs*. Angular Naphthalenes in Aromatic Tetradehydro Diels-Alder Reaction: Effect of Linker Structure and Steric bulk

Bhavani Shankar Chinta and Beeraiah Baire*[a]

Abstract: We report here a systematic study on the aromatic tetradehydro Diels-Alder (Ar-TDDA) reaction to understand the factors which may play key role on the distribution of linear and angular naphthalene products. Two factors such as nature of structure of the linker and steric bulk of the substituent on the enyne part have been studied. It is found that the structure of the linker has tremendous role on the product distribution. The effect of steric bulk of the substituent is dependent on the linker structure, in other words, shows different preferences for different linkers.

Introduction

Cycloaddition reactions are the 100% atom-economical protocols for the generation of poly substituted six-membered ring systems from corresponding acyclic precursors.[1] One of the most utilized and best examined cycloaddition is the [4+2] cyclization, known as the Diels-Alder (DA) reaction (Figure 1).[2] In a classical D-A reaction the 4π-electron component is referred to as "the diene" and the 2π- component as "the dienophile". If one or more double bonds in each of the diene and dienophile component are replaced by a triple bond, then we will have more unsaturated, in other words, dehydrogenated 4π and 2π components as partners in the Diels-Alder reaction. These are the "dehydrogenated" variants of the classical D-A reaction and hence called as dehydro Diels-Alder (DDA) reactions. Replacement of one double bond in each of the diene and dienophile component by triple bond will result in an enyne and an alkyne as 4π and 2π components respectively. The [4+2] cycloaddition reaction between an enyne and an alkyne is well studied. This reaction results in a cyclic allene, which would undergo a [1,5]H shift to generate the stable benzene/arene ring (Figure 1B). According to unsaturation, when compared to classical Diels-Alder reaction, the above transformation can be called as a tetradehydro Diels-Alder reaction (TDDA), but in the literature they are commonly referred as dehydro-Diels-Alder (DDA) reactions.[3] Throughout this manuscript we use the term TDDA reaction for this version. Recently, new variants of dehydrogenated or unsaturated Diels-Alder reactions namely, hexa-dehydro Diels-Alder (HDDA) reaction[4] and penta-dehydro Diels-Alder reaction[5] were also reported.

The ene component of an enyne part in the TDDA reaction can either be an acyclic olefin or cyclic olefin or can be a part of aromatic(benzene) ring. First two cases will result in substituted benzene and linearly fused tricyclic benzene derivatives respectively (Figure 1B). But in the third case (Figure 2), where the ene component is a part of benzene ring, i.e. arenyne **1**, there are always two products isolated in the literature, viz. linearly fused naphthalene **2** and angularly fused naphthalene **3** in varying amounts. A well accepted mechanism[6] for the formation of these two products **2** and **3** is shown in scheme **1**.

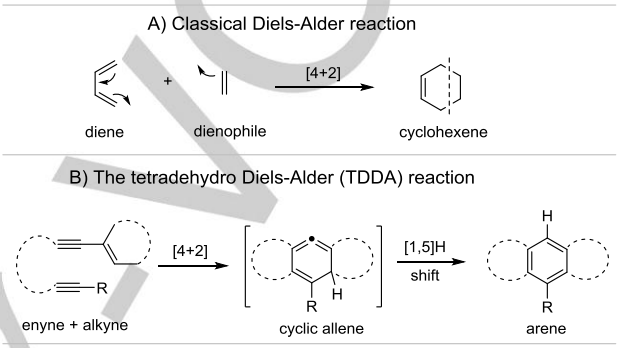

Figure 1: A) The classical [4+2] cycloaddition reaction, i.e., Diels-Alder reaction; B) The tetradehydro Diels-Alder (TDDA) reaction

According to this, there are two pathways (a and b) possible after the generation of the linear cyclic allene intermediate **4**, *via* an initial [4+2] cycloaddition between arenyne and alkyne. In path a, the allene **4** can directly undergo a [1,5]H shift to give the linear naphthalene product **2**. On the other hand, (path b) the same allene **4** can also undergo an electrocyclic ring opening process to give a (*Z*, *E*)-dehydro[10]annulene intermediate **5**. An isomerisation of **5** *via* C6-C7 σ-bond rotation, will generate the isomeric (*E*, *Z*)-dehydro[10]annulene intermediate **6**. Next, **6** can undergo an electrocyclic ring closing reaction to give the angular cyclic allene **7**, which will after [1,5]H shift generates the angular naphthalene **3**.

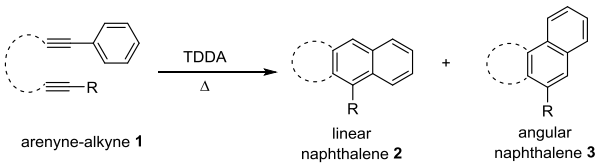

Figure 2: The aromatic tetradehydro Diels-Alder reaction

Based on this mechanism we propose that, the linear vs. angular product distribution in aromatic TDDA may depends on factors such as,

a) the nature or structure of the linker. This should have a considerable effect on the electrocyclic ring opening and closing processes, C-C bond rotations and sigmatropic [1,5]H shift.

b) the steric bulk of a substituent on the linker, in particular α-carbon of the enyne unit, will also play a critical role in controlling the rates of both the sigmatropic [1,5]H shifts by generating the repulsive steric hindrance with the "H" which comes after the [1,5]H shift in both the products.

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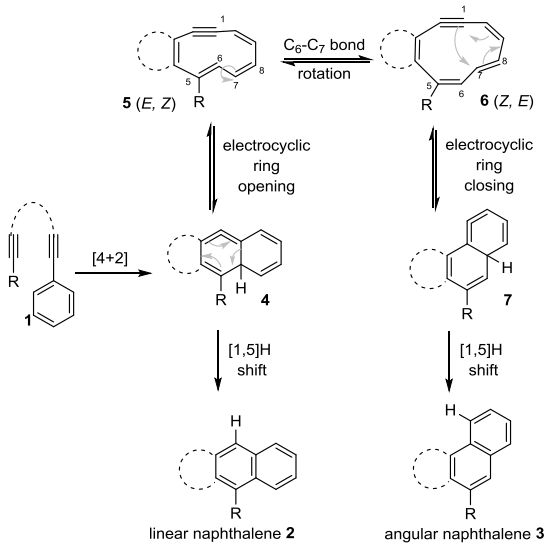
With this hypothesis, we aimed to perform a systematic study to delineate the role of above mentioned factors on the distribution of linear and angular products in the aromatic TDDA.



Scheme 1: Reported mechanism for the formation of linear and angular naphthalenes during the Ar-TDDA reaction

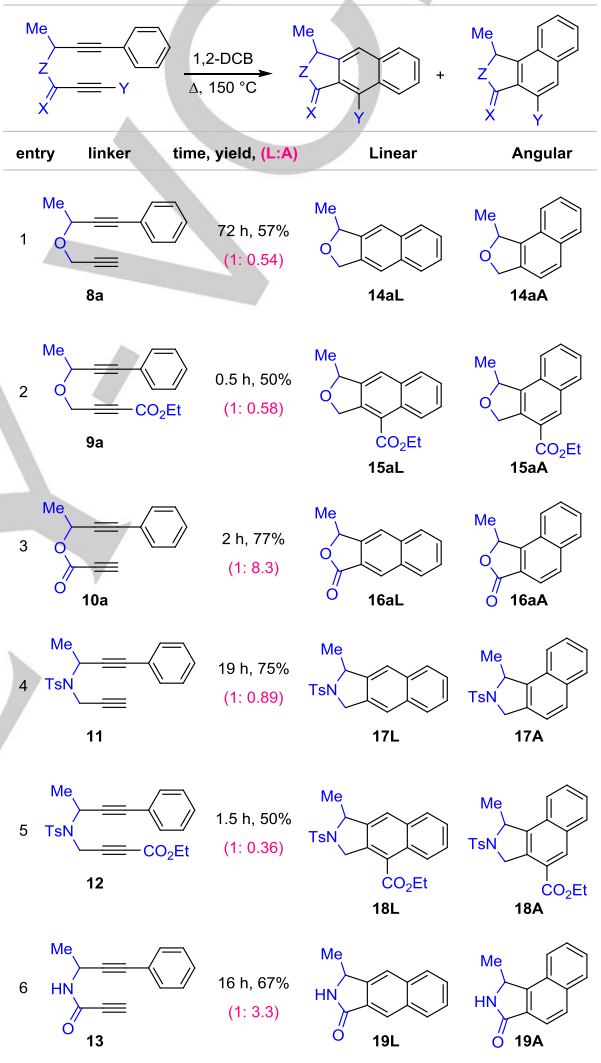
Results and Discussion

We initiated our study with the variation of linker structure. Accordingly, we prepared six arenyne-alkyne substrates **8a-10a** and **11-13** which possess six different linker structures. Each substrate was subjected to thermal heating conditions at same temperature (150 °C) in 1,2-dichlorobenzene (1,2-DCB) and results are presented in Table 1. In case of ether linker **8a**, the reaction (entry 1) resulted in a (1:0.54) mixture of both linear product **14aL** and angular product **14aA** respectively. The ynoate and ester linkers **9a** & **10a**, upon heating at 150 °C in 1,2-DCB gave (1:0.58) and (1: 8.3) ratios of corresponding linear and angular products (**15aL**:**15aA**) and (**16aL**:**16aA**) respectively (entry 2 & 3, Table 1). From the above three experiments of three differently activated oxygen based linkers, it is clear that the externally activated substrates (like ynoates) favour the linear products, whereas internally activated linkers such as esters, show preference for the angular products.

We next studied the behaviour of three more linkers' **11-13**, i.e., tosylamide, tosylamido-ynoate and imide. When substrate **11** was subjected to reaction conditions at 150 °C (entry 4, Table 1) the preference for the angular product **17A** increases when compared with its oxygen counterpart (entry 1, Table 1). The substrate **12** (amido-ynoate linker) provided a products ratio of (1:0.36) [**18L**:**18A**] relatively more preference towards the linear product than that of the oxygen linker (**9a**, entries 5 & 2). The imide linker **13**, under thermal conditions (entry 6, Table 1) gave a decreased preference for the angular product **19A** over the linear product **19L** (1:3.3), when compared with its oxygen counterpart **10a**, i.e., ester linker [entry 3, L:A = (1:8.3)].

From these experiments it is observed that the product preference trend in oxygen and nitrogen linkers of similar connectivity is in same direction. It is noteworthy to mention here that, different activation modes (outer *vs*. inner) on the linker exhibits completely reverse preferences for the cyclized products. The outer activation of the linkers e.g., entries 2 & 4 shows high preference for linear products, whereas the inner activation of the linkers i.e., entries 3 & 6, provides a very high preference for the angular products. Therefore, the product distribution in aromatic TDDA reaction showed much dependence on the structure of the linker and mode activation.

Table 1: Effect of linker structures on the linear *vs*. angular product distribution



In continuation, we aimed to evaluate also the effect of steric hindrance on the product distribution, which is created by the bulkiness of a substituent on the linker, in particular α-carbon of the enyne unit. It is proposed that (Figure 3) the [1,5]H shift from linear cyclic allene **4a** to linear naphthalene **2a** should be relatively less hindered by the steric bulk of the substituent "G" than the [1,5]H shift from angular cyclic allene **7a** to angular naphthalene **3a**. To verify this hypothesis, a study was performed on various linkers carrying substituent's with diverse steric bulk, on them employing standard conditions (150 °C in 1,2-DCB).

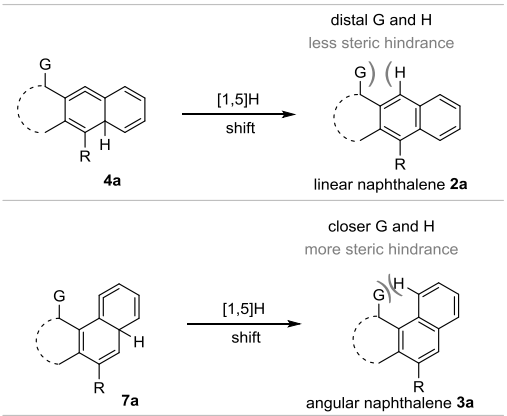
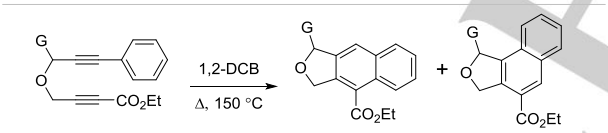


Figure 3: Possible steric hindrance by a substituent on the α-carbon (towards arenyne) of a linker

Initially an alkoxy-ynoate linker was employed (Table 2). In case of unsubstituted linker **9b** (G = H), the ratio of the products **15bL: 15bA** is (1:0.31). As the steric bulk of the substitutent increases from R = H to methyl to ethyl (entries 1-3, Table 2); the preference for the corresponding angular products **15aA** and **15cA** increases from 0.31 to 0.58 to 0.65. Surprisingly, further increase in the steric bulk by introducing the larger substituent's such as *iso*-propyl, *iso*-butyl, and cyclohexyl, (**9d, 9e & 9f**) resulted in the gradual decrease in the preference for the corresponding angular products **15dA-15fA** (entries 4-6, Table 2). In case of *tert*-butyl group (the bulkiest substituent) i.e., **9f** exclusive formation of linear product **15gL** was observed, and there was no detection of the corresponding angular product **15gA**.

Table 2: Estimation of steric bulk effect on the product distribution with externally activated linker

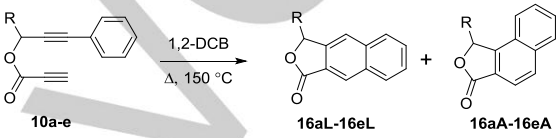


entry	enyne-alkyne	G	time (h)	product	yield (%)	ratio (**L** : **A**)
1	**9b**	H	0.5	**15b**	57	(1: 0.31)
2	**9a**	Me	0.5	**15a**	50	(1: 0.58)
3	**9c**	Et	0.5	**15c**	53	(1: 0.65)
4	**9d**	*i*Pr	0.5	**15d**	60	(1: 0.55)
5	**9e**	*i*Bu	0.5	**15e**	64	(1: 0.26)
6	**9f**	cyclohexyl	0.5	**15f**	57	(1: 0.27)
7	**9g**	*t*-Bu	0.5	**15g**	67	only **15gL**

These observations suggests that, the initial increase in the steric hindrance might slow down the [1,5]H shift of the linear cyclic allene **4a** to linear product **2a** and hence the competing electrocyclic ring opening process is relatively more favoured towards the formation of angular allene **7a**. Therefore, the preference for angular product **3a** increases over the linear product **2a**. But after a certain threshold level of steric hindrance, the increased steric bulk might be creating relatively stronger hindrance for the [1,5]H shift of the angular cyclic allene **7a** to angular product **3a** when compared with the [1,5]H shift of the linear cyclic allene **4a** to linear product **2a** and hence the preference for the angular products decreases.

Subsequently, the ester linker (internal activation) with various substituent's was also employed to verify the steric bulk effect (Table 3). Heating different enyne-alkynes **10a-10c** at 150 °C in 1,2-DCB resulted in the highly preferred formation of angular products **16aA-16eA** over their linear counterparts **16aL-16eL** (entries 1-5). As the steric bulk increases from H to -Me to -Et to -^{i}Pr to -^{t}Bu, there was no noticeable change observed in the product distributions as the ratios of L:A lies between (0.12:1) to (0.15: 1).

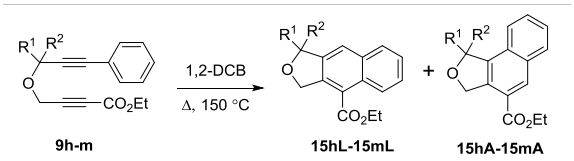
Table 3: Estimation of steric bulk effect with internally activated linker



entry	enyne-alkyne	R	time (h)	product	yield (%)	ratio (**L** : **A**)
1	**10b**	H	2	**16b**	66	(0.12 : 1)
2	**10a**	Me	2	**16a**	77	(0.12 : 1)
3	**10c**	Et	2	**16c**	77	(0.15 : 1)
4	**10d**	*i*Pr	2	**16d**	77	(0.14 : 1)
5	**10e**	*i*Bu	2	**16e**	47	(0.20 : 1)

Furthermore, we turned our attention to estimate the steric effect of quaternary centres on the linkers. Accordingly, alkoxy-ynoate linker with various α,α-disusbstitutions (quaternary centres) was examined. All these substrates **9h-9m** show the preference for the linear products **15hL-15mL** over angular products **15hA-15mA** similar to the case of single substituent's (Table 2). There was no drastic change in the distribution of products has been observed.

Table 4: Steric bulk effect of quaternary centres on externally activated linker

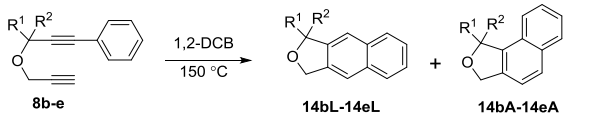


entry	enyne-alkyne	R^1 & R^2	time (h)	product	yield (%)	ratio (**L** : **A**)
1	**9h**	Ph, Me	0.5	**15h**	80	(1: 0.36)
2	**9i**	Ph, Et	0.5	**15i**	82	(1: 0.22)
3	**9j**	Ph, Ph	0.5	**15j**	70	(1: 0.24)
4	**9k**	Ph, Bn	0.5	**15k**	53	(1: 0.46)
5	**9l**	-$(CH_2)_5$-	0.5	**15l**	57	(1: 0.31)
6	**9m**	cyclopropyl, Me	0.5	**15m**	53	(1: 0.39)

In continuation we performed the same study on an inactivated ether linker with different quaternary centres (entries 1-4, Table 5). Surprisingly, all the substrates **8b-e** resulted in the exclusive formation of corresponding linear products **14bL-14eL**. There was no detection of any of the angular products **14bA-14eA**. This supports the fact that, after certain level of steric bulk threshold,

irrespective of the linker, the linear products are more preferred than their angular counterparts.

Table 5: Steric bulk effect of quaternary centres on inactivated ether linker



entry	enyne-alkyne	R^1 & R^2	time (h)	yield (%)	product	ratio (**L** : **A**)
1	**8b**	Ph, Me	18	75	**14bL**	(1 : 0)
2	**8c**	Ph, Et	18	60	**14cL**	(1 : 0)
3	**8d**	Ph, Ph	20	80	**14dL**	(1 : 0)
4	**8e**	Ph, Bn	16	67	**14eL**	(1 : 0)

Overall the linear *vs*. angular product distributions during aromatic TDDA reactions did show little dependency on the steric bulk of the substituent, on the other hand, it depends strongly on the structure of the linker of the enyne-alkyne unit.

Conclusions

In conclusion we have performed a systematic study to understand the effect of two factors such as a) nature of the linker structure, b) steric bulk created by the of the substituent on the α-carbon of enyne linker, on the distribution of linear *vs*. angular naphthalene product during the aromatic tetradehydro Diels-Alder reaction. From this study it is evident that, the nature of the structure of linker plays a very strong role on the product distributions, where different linkers show preference for the different products, i.e. linear *vs*. angular. Within the same linker the internal activation favours the angular products whereas the external activation favours the linear one. The steric bulk of the substituent on the linker does not have any strong as well as consistent role on the product distributions. Nevertheless no substituent linkers show high preference for the linear naphthalenes, whereas gradual increase in steric hindrance favours the angular product up to certain level and then reverse the preference towards linear.

Experimental Section

General experimental procedure for the synthesis of 1,3-Dihydronaphtho[2,3-c]furan (14a) through tetradehydro Diels-Alder reaction.

To a solution of alkyne 8 (70 mg, 0.411 mmol) in 1,2-DCB (7 mL) was taken in a reaction tube. The reaction tube was kept at 150°C. After 114 h, the reaction mixture was purified by column chromatography (9:1, hexane:EtOAc) gave the 14L (35 mg, 0.205 mmol, 50 %) as a yellow solid.

For full details of all experiments, see the Supporting Information.

Acknowledgements

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Keywords: alkynes • cycloadditions • dehydrogenative Diels-Alder reactions • enynes • linkers •

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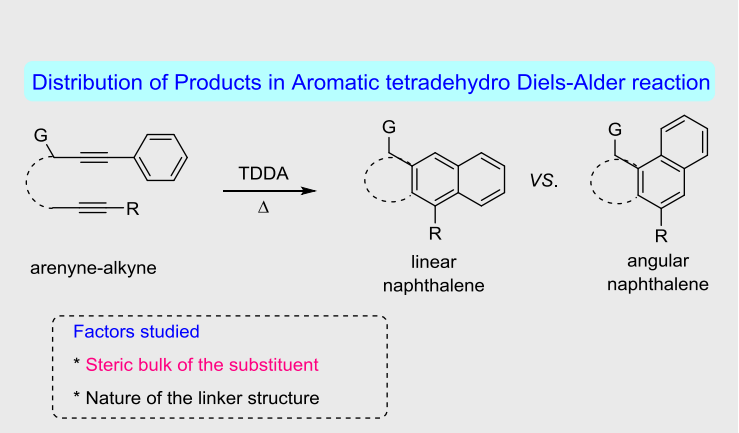

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