Analysis of geometric and strain effects in homo-Diels–Alder reactions

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Abstract. Molecular mechanics calculations have been carried out to quantify the key geometric and strain effects which are likely to control the homo-Diels–Alder reactivity of 1,4-dienes. The criteria considered include C1..C5 and C2..C4 distances in the diene, twist angle of the two π units, and the magnitude of strain increase as a result of cycloaddition. By first considering these factors in a number of non-conjugated dienes with known reactivity, the ranges of values within which the reaction is favoured are proposed. Calculations are also reported on several substrates which have not been investigated so far. Promising systems for experimental study are suggested which, in addition to being intrinsically interesting, would place the present proposals on a firm basis.

Keywords. Homo-Diels–Alder reaction; molecular mechanics; strain; modelling.

1. Introduction

The homo-Diels–Alder (HDA) reaction involving a non-conjugated 1,4-diene and a dienophile is a potentially useful method for the synthesis of bridged polycyclic compounds, producing two C–C σ bonds and a cyclopropane ring in one step (scheme 1). The reaction, known for over 3 decades (Ullman 1958; Blomquist and Meinwald 1959; Hall 1960; Cristol *et al* 1962; Cookson and Dance 1962; Moriarty 1963; Cookson *et al* 1964; Schrauzer and Glockner 1964; Huebner *et al* 1966; Tufariello *et al* 1966; Sasaki *et al* 1972), represents a specific example of a more general class of [2 + 2 + 2] cycloadditions. However, compared to the Diels–Alder reaction, the mechanistic details of the HDA reaction are less understood and the methodology is underexploited in organic synthesis.

The reaction is generally thought of as a sluggish process lacking stereo-electronic control. The reactants involve non-conjugated species and hence are not amenable to electronic activation. While stereospecificity and concerted pathways have indeed been proposed in certain cases (Kobuke *et al* 1972; Tabushi *et al* 1975; Jenner and Papadopoulos 1982), and regioselectivity in cobalt-catalyzed reactions (Lautens and Edwards 1991), the reaction in general is likely to involve biradicaloid intermediates. The factors which determine HDA reactivity are therefore likely to be purely geometric in nature.

The first systematic investigation of the scope of the HDA reaction involving various dienes with a common reactive dienophile confirmed the above view (Fickes and Metz 1978). The ease of reaction of <u>1</u>–<u>7</u> with tetracyanoethylene (TCNE) was suggested to be

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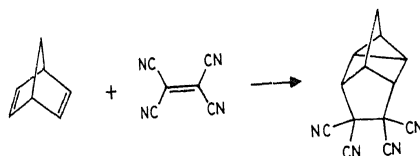
Scheme 1. Representative homo-Diels–Alder reaction.
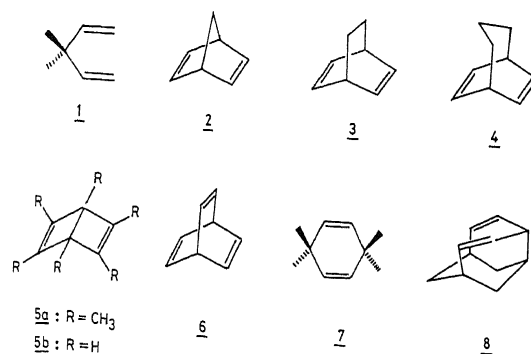
inversely related to the distance between the double bonds estimated from models. Only two exceptions were noted. The unreactive nature of acyclic $\underline{1}$ was attributed to the unfavourable entropic term. For $\underline{7}$, estimates of strain energies indicated that the formation of a three-membered ring is highly unfavourable.

The presence of an additional factor controlling HDA reactivity was revealed by the facile reaction of tricyclo $[5\cdot3\cdot1\cdot0^{4,9}]$undeca-2,5-diene, $\underline{8}$ with TCNE (Yamaguchi *et al* 1984). Both MM2 and *ab initio* (STO-3G) calculations indicated a fairly large separation between the reactive sites of the diene ($\approx 3\cdot4$ Å). The remarkable reactivity of $\underline{8}$ was explained on the basis of the mutual orientation of the π bonds. The π lobes are directed towards each other allowing for strong through-space interactions. The orbital tilt is also ideally suited for maximising overlap with an approaching dienophile. It was concluded that close proximity of the double bonds is not a prerequisite for significant HDA reactivity.

In this paper, we attempt to place geometric and strain factors which determine the feasibility of HDA reaction on a quantitative basis. Molecular mechanics calculations have been used for this purpose. First, several dienes which have been experimentally examined are considered. After obtaining general criteria for HDA reactivity, additional systems not yet experimentally studied are evaluated. Suitable substrates for further investigation to quantify our proposals are suggested.

2. Results and discussion

2.1 *Computational model*

Geometry optimisation using the MM2 force field (Allinger 1977) was carried out on a number of non-conjugated dienes. The reactivity of the dienes towards TNCE or related activated dienophiles was correlated with specific structural parameters. Among the various possible factors which can influence HDA reactivity, the $C_1..C_5$ and $C_2..C_4$ distances of the 1,4-diene (figure 1a) are important. Shorter distances will
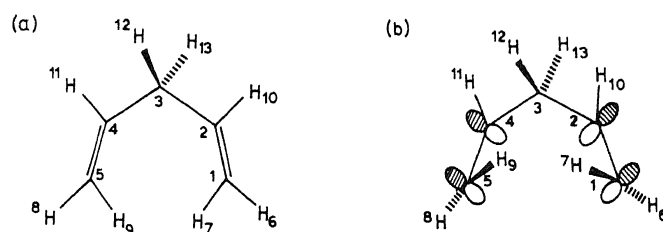
(a) (b)

Figure 1.(a) Atom numbering for a representative 1,4-diene used in the definition of geometrical parameters in the text. **(b)** Twist at the terminal carbon atoms which would favour stabilising orbital interactions with an approaching dienophile.

enhance through-space interactions between the double bonds. Further, the terminal carbon atoms of the diene would be ideally poised for interaction with the approaching dienophile, while the internal carbon atoms can form a new C–C bond more readily.

The mutual alignment of the double bonds is also a key factor which determines through-space interactions and the ability to interact with a dienophile. The relative orientations of the π lobes of a double bond at each carbon centre can be quantified by two dihedral angles, viz., the inner tilt angle and the outer tilt angle, which we define as follows (figure 1a). At the terminal carbon atoms (at C_1 and C_5), the inner tilt angles (Φ_{1i}) are the dihedral angles $H_7 C_1 C_2 C_4$ and $H_9 C_5 C_4 C_2$. For a symmetrical diene the absolute values of these two dihedral angles are equal. Similarly the outer tilt angles (Φ_{1o}) are chosen as the dihedral angles $H_6 C_1 C_2 C_4$ and $H_8 C_5 C_4 C_2$, whose absolute values are again equal for a symmetrical diene. When the π lobes at the terminal carbon atoms (at C_1 and C_5) of the diene are parallel to each other and have the least direct overlap, the inner tilt angles are zero and the outer tilt angles are $180°$. As the inner tilt angle increases and the outer tilt angle correspondingly decreases, the p-lobes of the double bonds at the terminal carbon atoms are twisted towards each other (see figure 1b). This is favourable for HDA reactivity because the diene can interact strongly with the approaching dienophile.

The C_1–C_2 and C_4–C_5 bonds are not necessarily parallel in most 1,4-dienes. In typical unsymmetrical structures, intramolecular through-space interactions involving the internal carbon atoms C_2 and C_4 will be larger than those involving the terminal atoms C_1 and C_5. Therefore, it is important to consider the mutual orientation of the $p(\pi)$-lobes at C_2 and C_4 also. The relative alignment can be quantified by the inner and outer tilt angles in a way similar to that done in the case of terminal carbon atoms. Thus, the inner tilt angles (Φ_{2i}) are $C_3 C_2 C_1 C_5$ and $C_3 C_4 C_5 C_1$ dihedral angles, while the outer tilt angles (Φ_{2o}) are $H_{10} C_2 C_1 C_5$ and $H_{11} C_4 C_5 C_1$ torsion angles. For a symmetrical diene, such as $\underline{2}$, the absolute values of both the inner tilt angles as well as the outer tilt angles are equal. The through-space interaction between the p-lobes at the internal carbon atoms is maximum if the inner and outer tilt angles are $-90°$ and $90°$ respectively.

Since a cyclopropyl ring is formed in the HDA reaction, strain effects also need to be assessed. Molecular mechanics provides a sound basis for studying such effects. The increase in strain energy on going from the diene to the HDA adduct using ethylene as a model dienophile (ΔE_{strain}) has been calculated for various 1,4-dienes.

The calculated distances, tilt angles and strain energy changes for cycloadduct formation for $\underline{1}$–$\underline{7}$ are given in table 1. The data provide a quantitative basis for evaluating the reactivity of the dienes with a common dienophile. For a direct

Table 1. MM2 geometric parameters and the increase in strain energy (ΔE_{strain}) on going from the diene to the homo-Diels–Alder adduct for various 1,4-dienes. Bond lengths in Å; angles in degrees; strain energy in kcal/mol.

1,4-Diene	$C_1..C_5$ (Å)	$C_2..C_4$ (Å)	Φ_{1i}	Φ_{1o}	Φ_{2i}	Φ_{2o}	ΔE_{strain}
1	3·41	2·45	38	− 141	− 37	141	30·2
2	2·40	2·40	33	− 145	− 33	145	21·3
3	2·39	2·39	29	− 151	− 29	151	31·9
4	2·41	2·41	24	− 156	− 24	156	43·6
5a	2·58	2·58	30	− 148	− 30	148	30·5
5b	2·60	2·60	30	− 149	− 30	149	34·2
6	2·38	2·38	30	− 149	− 30	149	24·0
7	2·51	2·51	1	− 179	− 1	179	46·5
8	3·46	2·31	51	− 130	− 45	130	31·5

assessment, a summary of available experimental information on HDA reactions involving these dienes is provided in table 2 (Blomquist and Meinwald 1959; Krespan *et al* 1961; Zimmerman and Swenton 1964; Grant *et al* 1965; Sasaki *et al* 1972; Iwamura *et al* 1976; Fickes and Metz 1978; Yamaguchi *et al* 1984b). Since the experimental studies have been carried out under different conditions, the data are used only to make a qualitative judgement of the ease of homo-Diels–Alder reaction of the various substrates.

2.2 Analysis of systems with known reactivity

The calculated results in table 1 are of considerable interpretive value. The data have a more quantitative basis than the previous analysis (Fickes and Metz 1978) using Dreiding models. Interestingly, among the bicyclic dienes 2–4, the variation in the $C_1..C_5$ distance is not as large as had been suggested by these authors. Hence, the importance of this factor in these dienes had been overemphasized. On the basis of MM2 calculations, the geometric factors are quite similar in these dienes. The key difference is found in the strain energy increase on HDA addition. While the increase is only 21 kcal/mol for norbornadiene, it becomes progressively larger, by over 10 kcal/mol, for the bicyclooctadiene (3) and the bicyclononadiene (4) derivatives. Therefore, the rapid fall in the HDA reactivity of these dienes with TCNE may be understood on the basis of the strain factor alone. The geometric and strain factors computed for the Dewar benzenes (5a, b) and barrelene (6) are also within the acceptable range for facile homo-Diels–Alder reaction.

As pointed out earlier (Yamaguchi *et al* 1984b), the reactivity of the tricyclic diene 8 can be understood in terms of the significant tilt of the π lobes towards each other. The data in table 1 provide a useful comparison. Among the various dienes shown in table 1, the inner tilt at the terminal carbon atom is the largest (51°) for 8. The inner tilt at the internal carbon atom is also quite large (− 45°) to produce strong through-space interactions between the double bonds. The strain energy increase, although larger than in 2, is comparable to that obtained for the relatively reactive diene 3. These favourable factors enable the diene to be reactive towards TCNE in spite of a relatively large separation of 3·46 Å between the terminal olefinic carbon atoms.

Table 2. Reaction conditions and yields for the homo-Diels–Alder reactions of several 1,4-dienes with various dienophiles.

1,4-Diene	Dienophile	Reaction conditions* time/temp(h/°C)	Solvent	Yield[+] (%)
1	TCNE	52/145	C_6H_6	No rxn
2	TCNE	0·5/rflx	C_6H_6	100
	Dimethylacetylene-dicarboxylate	12/rflx	C_6H_6	50
	Cyanoacetylene	40/145	None	31
	Cyanoacetylene	69/90	C_6H_6	26
	N-t-butyl-propiolamide	100/165	None	Very low
	Chlorocyano-acetylene	40/80	C_6H_6	50
3	TCNE	30/rflx	C_6H_6	85
	TCNE	11/100	C_6H_6	53
	Dimethylacetylene-dicarboxylate	36/100	C_6H_6	No rxn
4	TCNE	15/145	C_6H_6	24
	Dimethylacetylene-dicarboxylate	24/150	C_6H_6	No rxn
5a	TCNE	Reflux	C_6H_5Cl	85
6	Dicyanoacetylene	RT		95
7	TCNE			No rxn
8	TCNE	1/rflx	C_6H_6	100
	Maleic anhydride	12/rflx	o-$C_6H_4Cl_2$	81
	Dimethylacetylene-dicarboxylate		o-$C_6H_4Cl_2$	22

*rflx = reflux; + "No rxn" indicates "no reaction"

It is known that 3,3-dimethyl-1,4-pentadiene (1) and 3,3,6,6-tetramethyl-1,4-cyclohexadiene (7) do not undergo the HDA reaction even with the highly activated dienophile TCNE (table 2). MM2 calculation shows that 3,3-dimethyl-1,4-pentadiene has a $C_1..C_5$ distance of 3·41 Å and a strain energy increase of 30 kcal/mol. These values are comparable to those obtained for the reactive diene 8. The tilt angles at the terminal carbon atoms (38° and − 148°) as well as at the internal carbon atoms (− 37° and 141°) also suggest reasonable mutual alignment of the π lobes for favourable overlap. Therefore the failure of 1 to undergo the HDA reaction with TCNE may be due to the entropic factor, as suggested before (Fickes and Metz 1978). In the case of 7, only the distance criterion for efficient HDA reaction is met (table 1). The ground state geometry of the diene is planar at the MM2 level, in agreement with *ab initio* calculations (Birch *et al* 1981). Hence the absence of any tilt of the double bonds precludes significant through-space interactions. The unfavourable strain effect postulated earlier (Fickes and Metz 1978) on the basis of rates of model reactions is also confirmed by the present calculations. The increase in strain following addition to 7 is

greater than 46 kcal/mol. The non-reactivity of this diene with TCNE is consistent with the MM2 results.

On the basis of the above comparison of calculated parameters and experimental results, a set of guidelines can be proposed for predicting the HDA reactivity of a non-conjugate diene. The $C_2..C_4$ distance is relatively unimportant. Dienes with a $C_1..C_5$ separation of even 3·5 Å can be reactive provided there is sufficient tilt of the π lobes at the internal and terminal carbon atoms. The increase in strain following addition should not exceed 40 kcal/mol.

The above criteria were tested against the known reactivity pattern of 1,3,5,7-tetramethylenecyclooctane ($\underline{9}$) towards dienophiles. In principle, the molecule $\underline{9}$ can undergo a homo-Diels–Alder type addition to give $\underline{10}$ or a $2 + 2 + 2$ cycloaddition involving the exocyclic double bonds at C1 and C5 to yield $\underline{11}$ (scheme 2). Experimentally, only the latter mode of cycloaddition is observed (Williams and Benson 1962). This can be rationalised on the basis of geometric and strain considerations.

Three conformations are reasonable for $\underline{9}$ (figure 2). In the D_{2d} form $\underline{9a}$, the exocyclic double bonds at C1 and C5 are oriented ideally for interaction with an approaching dienophile. In contrast, the geometry of the C_{2h} conformer, $\underline{9b}$, permits only a homo-Diels–Alder type cycloaddition. Both cycloaddition modes are possible, in principle, for conformer $\underline{9c}$ with C_{4v} symmetry. All three forms were optimised at the MM2 level. Strain energy changes for cycloaddition to ethylene were also computed.

The requirements for homo-Diels–Alder reaction are fairly met in conformer $\underline{9b}$ (table 3). The terminal carbon atoms are separated by 3·4 Å, while the internal carbon atoms are 2·5 Å apart. The π bonds are partially tilted towards each other and the strain energy increase for cycloaddition is modest (table 3). However, this conformer is the least stable of the three considered ($\Delta H_f = 52·5$ kcal/mol).

The homo-Diels–Alder mode should be favoured in the more stable form $\underline{9c}$ also ($\Delta H_f = 48·6$ kcal/mol), although the criteria are slightly less favourable than in $\underline{9b}$ (table 3). The double bonds at C1 and C5 are too widely separated (terminal distance = 5·1 Å, internal distance = 3·5 Å) to favour the formation of $\underline{11}$.

The preferred formation of $\underline{11}$ is supported by the geometry and strain of the most stable conformation $\underline{9a}$ ($\Delta H_f = 45·9$ kcal/mol). The terminal carbon atoms of the reactive ends of $\underline{9a}$ have the least separation of the three conformers considered (3·17 Å), while the internal carbon atoms are also quite close, 2·79 Å (table 3). Further,
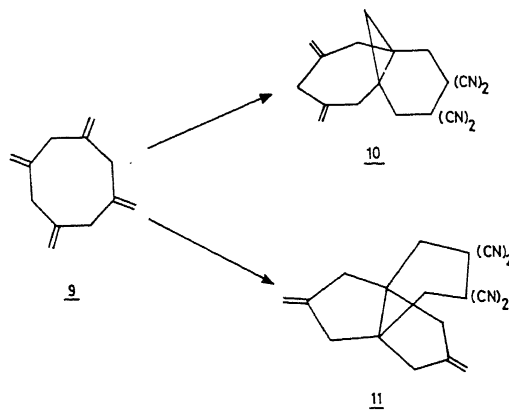
Scheme 2. Possible cycloaddition modes of $\underline{9}$ with TCNE
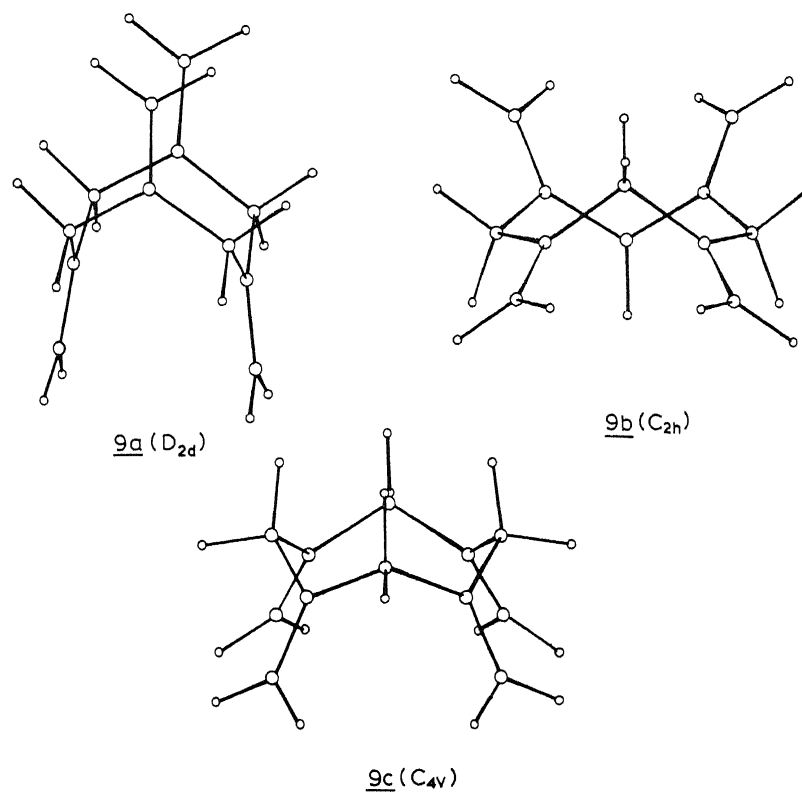
9a (D$_{2d}$)

9b (C$_{2h}$)

9c (C$_{4v}$)

Figure 2. Three optimised conformations of tetraene $\underline{9}$.

Table 3. MM2 geometric parameters and the increase in strain energy (ΔE_{strain}) for cycloadduct formation for various conformations of $\underline{9}$.
r in Å; angles in degrees; strain energy in kcal/mol.

Conformer	r_{term}	r_{inner}	Φ_{1i}	Φ_{1o}	Φ_{2i}	Φ_{2o}	ΔE_{strain}
$\underline{9a}$	3·17	2·79	90	−90	−90	90	17·0
$\underline{9b}$	3·40	2·51	34	−145	−34	145	21·9
$\underline{9c}$	3·59	2·48	39	−140	−39	140	23·2

the π bonds are favourably oriented towards each other (figure 2). Most importantly, the $2 + 2 + 2$ cycloaddition reaction does not lead to the formation of a 3-membered ring, but to a less strained 5-membered ring. The overall strain energy increase on cycloaddition is just 17·0 kcal/mol. Thus, all geometric and strain energy criteria clearly favour this mode of reaction.

2.3 *Predictions for new substrates*

It would be of considerable interest to critically evaluate the above proposals with additional dienes. In particular, the outer limits for the distance criterion and the strain factor need to be evaluated. With these goals in mind, we have computed the geometric

and energetic factors of importance in HDA reactivity for a number of non-conjugated dienes which have not been studied experimentally. After an analysis, the systems ideally suited for further study which would enable a quantitative definition of the scope of the HDA reaction are identified.

Two series of 1,4-dienes have been considered. The first is a set of bicyclo [3·3·n] dienes (12–15). These are clearly related to the bicyclic dienes 2–6 which have been studied extensively. The second is a set of relatively rigid molecules (16–21) in which the terminal units of the diene are geometrically capable of responding flexibly to a dienophile. In our terminology, the inner and the outer tilt angles at the terminal carbon atoms are not constrained by the ring skeletons in these systems. The calculated MM2 geometric parameters of interest and the increase in strain energy due to HDA addition for the two series of compounds are provided in table 4.

The MM2 results in table 4 show that the series of bicyclo [3·3·n] dienes (12–15) have $C_1 .. C_5$ distances of 3·5 Å or more. The values are significantly larger compared to those

Table 4. MM2 geometric parameters and the increase in strain energy (ΔE_{strain}) on going from the diene to the homo-Diels–Alder adduct for additional 1,4-dienes. Bond lengths in Å; angles in degrees; strain energy in kcal/mol

1,4-Diene	$C_1 .. C_5$ (Å)	$C_2 .. C_4$ (Å)	Φ_{1i}	Φ_{1o}	Φ_{2i}	Φ_{2o}	ΔE_{strain}
12	3·85	2·50	35	−143	−30	148	38·0
13	3·54	2·40	43	−137	−42	135	37·4
14	3·57	2·49	38	−142	−37	141	46·0
15	3·53	2·48	36	−143	−40	138	46·0
16	4·09	2·54	40	−139	−40	138	34·2
17	4·07	2·38	48	−131	−47	131	26·0
18	4·40	2·44	44	−135	−43	137	31·3
19	4·59	2·48	38	−140	−37	143	28·1
20	4·37	2·44	43	−135	−44	135	36·0
21	4·71	2·30	44	−136	−44	135	45·6
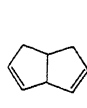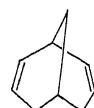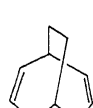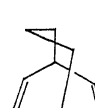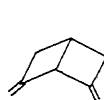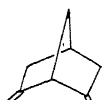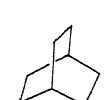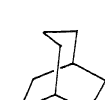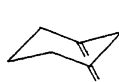
of the bicyclo [2·2·n] dienes (2–7) but close to the proposed upper limit of the parameter for observable HDA reactivity. Interestingly, the calculated tilt angles for the series are consistently more favourable compared to the series of bicyclo [2·2·n] dienes. However, the strain energy factor is calculated to be more unfavourable in the bicyclo [3·3·n] dienes than in the corresponding bicyclo [2·2·n] dienes. For example, bicyclo [3·3·1] nona-2,7-diene (13) is computed to have a strain energy increase of 37·4 kcal/mol (table 4), while the value for norbornadiene is only 21 kcal/mol (table 1). The increase in strain energy is much higher in dienes with larger methylene bridges.

On the basis of the above results, it would be worthwhile to examine the homo-Diels–Alder reactivity of bicyclo[3·3·1]nona-2,7-diene (13). If the molecule does undergo the reaction, the proposed empirical criteria would be validated.

The terminal $C_1..C_5$ distances in the next series of 1,4-dienes 16–21 considered in this study are found to be higher than in all the previously examined systems, being consistently more than 4·0 Å (table 4). However, the tilt angles are quite favourable in the exo-methylene derivatives compared to that of the bicyclic dienes 2–6 and the bicyclo[3·3·n] dienes 16–21. Further, the strain energy increases on HDA addition are also found to be relatively small. A particularly interesting case is the diene 2,6-dimethylidene-bicyclo[2·2·1]heptane (17) for which the increase in strain energy is only 26 kcal/mol. Although the $C_1..C_5$ distance is 4·07 Å in this system, on the basis of favourable tilt angles (48°, − 131° at terminal and − 47°, 131° at internal carbon atoms) and the relatively modest increase in strain energy, it is also a worthy candidate for experimental examination as a HDA substrate. If 17 is reactive, the limit for the $C_1..C_5$ distance of the 1,4-diene for HDA reaction needs to be extended. Also, a subsequent study of 18–20 may be attempted. In these dienes, the tilt angles and strain energy increases are within the limits proposed above. The only unfavourable feature is calculated to be the distance between the terminal carbon atoms. Hence, the reactivity of these systems would establish the upper bound for the geometric criterion for the HDA reaction.

3. Conclusions

Computed geometries and strain energies of several 1,4-dienes with known HDA reactivity suggest possible factors which may be crucial. Based on available experimental information, a few essential requirements for HDA reactivity have been proposed. The reactive dienes have a C1..C5 separation of less than 3·5 Å, tilt of π lobes of over 30° and modest strain energy increase (less than 40 kcal/mol) for cycloadduct formation. Additional substrates for experimental study are suggested to establish the limits more precisely and to enhance the scope of the HDA reaction. These proposals may be of use for a quick appraisal of potential HDA reactivity of a non-conjugated diene.

It would be of interest to evaluate the reliability of the criteria derived from molecular mechanics calculations by determining the geometries and energies of transition states for representative substrates through quantitative MO procedures. The results of these studies, currently underway, will be reported shortly.

Acknowledgement

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