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A COMPUTATIONAL STUDY TOWARDS THE REACTIVITY OF 2-(2-ETHYNYLPHENYL-X-)PYRIMIDINES IN INTRAMOLECULAR DIELS-ALDER REACTIONS.

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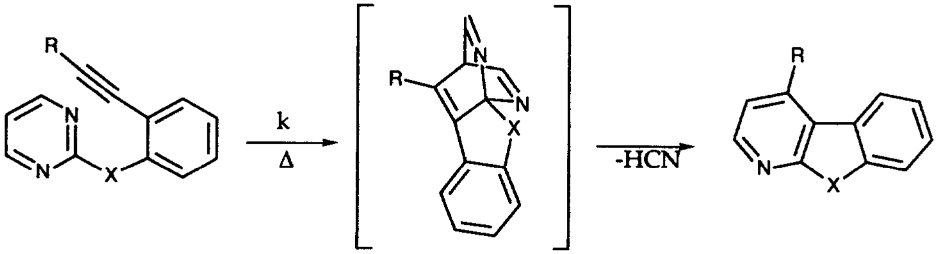
Abstract The reactivity of 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines towards intramolecular Diels-Alder reactions to give tricyclic annelated pyridines, decreases in the order X = CO >> O > CH_2 >> NH A conformational study (MM calculations) and determination of the heat of activation (MNDO calculations) of their 2-(2-ethynylphenyl-X-)pyrimidine analogs showed that the order of reactivity is reflected by the probability of the molecules to be in a conformation which is able to react

INTRODUCTION

In a previous paper, we described the inverse electron demand Diels-Alder reactions of 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines (X = O, S, NH, NAc, CH_2, CO) to give tricyclic annelated pyridines[1] (Scheme I)

By heating at 160 °C the 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines **1A**, with exception of X = NH, easily undergo an intramolecular Diels-Alder reaction with inverse electron demand to provide the tricyclic annelated pyridines **3A**, the observed order of reactivity is CO >> NAc > O > CH_2 > S >> NH In previous publications of our group and others[1,2,3] it was found that in this two step process the formation of intermediate **2** is the rate determining step, for it was never possible to detect this intermediate species This implies that the investigation towards the reactivity of the conversion of **1** can be focussed on the cycloaddition of **1** to **2**

Scheme I



1 **2** **3**

A. R = SiMe$_3$, **B** R = H
X = CO, O, CH$_2$, NH

In Table I the reaction rates of some typical 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines and the inductive effects of the corresponding phenyl-X-groups are listed The mesomeric effects are not listed because the strongly twisted shape of the intermediates **2** prevents any mesomeric interactions It is seen that the order of reactivity of these compounds cannot simply be explained by the order of the electron withdrawing ability of the X-group In order to get a better insight into the factors that determine the relative rates of the cycloadditions, we decided to carry out conformational analyses towards the 'reactive' conformations of the starting compounds (Molecular Mechanics calculations) Furthermore, the heats of activation of the rate determining Diels-Alder reaction of **1** to **2** for the various pyrimidine systems were calculated (MNDO calculations)

In previous studies of our group[4] it was found that silylated and desilylated alkyne groups react at comparable rates in Diels-Alder reactions with inverse electron demand, although the silylated compounds always react slightly slower, due to the bulkiness of the trimethylsilyl group Therefore the computationally more practical desilylated molecules **B** instead of the silylated pyrimidines **A** were used in this study

Table I Reactivity (k) at 160 °C of some typical 2-(2-trimethylsilylethynyl-phenyl-X-)pyrimidines **1A** and the inductive effects (σ_I) of the corresponding phenyl-X-groups

compounds **1A**	k^a	σ_I
X = CO	17 80	0 30
X = O	0 41	0 40
X = CH$_2$	0 23	0 04
X = NH	<0 001	0 30

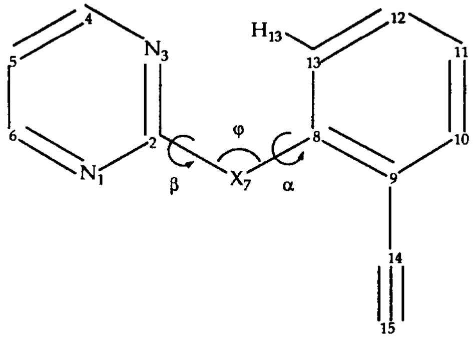
^{a} 10^{-3} s^{-1}

RESULTS AND DISCUSSION

Conformational analyses

In this investigation, the reactivity of the 2-(2-ethynylphenyl-X-)pyrimidines (see Figure I) will be studied by systematic changes in the geometry of the molecules To ensure that reliable starting geometries were used for the conformational analyses, the molecules **1B** (X = CO, O, CH_2, NH) were defined in the CHEMX-program[5a] and optimized in the MM force field[5b] (see Table II)

Figure I Atom numbering, definition of bond angle φ and torsion angles α and β of the 2-(2-ethynylphenyl-X-)pyrimidines **1B**



α C9-C8-X7-C2, β C8-X7-C2-N1, φ C8-X7-C2

For the conformational analyses, the 2-(2-ethynylphenyl-X-)pyrimidines are regarded as two-rotor molecules[6] (rotation around C2-X7 and X7-C8) and it is assumed that the various conformations considered are 'states' of the rigid rotor system[6,7,8] The bond distances C2-X7 and C8-X7, and the bond angle φ, used in these analyses, are listed in Table II The torsion angle α was rotated from -180 to 180 degrees and, due to the mirror symmetry of the 2-pyrimidyl part of the

Table II Some important conformational parameters of the optimized geometries of the 2-(2-ethynylphenyl-X-)pyrimidines **1B**

compounds	optimized values		
	φ[a]	d C2-X7[b]	d X7-C8[b]
X = CO	121 4	1 495	1 509
X = O	123 4	1 335	1 331
X = CH2	114 8	1 495	1 494
X = NH	127 8	1 337	1 342

[a]angles in degrees, [b]distances in Å

molecule, the torsion angle β was rotated from 0 to 180 degrees Using increments for α and β of 5 degrees, 2592 conformations were generated and their potential energies (E_i) calculated

Since all conformations are thermally accessable, the probability of a molecule to be in a particular conformation can be calculated as a function of the dihedral angles[6] α and β ($P_i(\alpha, \beta)$), using the Bolzmann distribution equation (1)

$$P_i(\alpha, \beta) = \frac{e^{\frac{-dE_i}{RT}}}{Q} \quad , Q = \sum_{i=1}^{n} e^{\frac{-dE_i}{RT}} \tag{1}$$

P_i = probability, $dE_i = E_i - E_0$, $R = 8\ 31\ J\ K^{-1}\ mol^{-1}$, $T = 433\ K$ (160 °C)

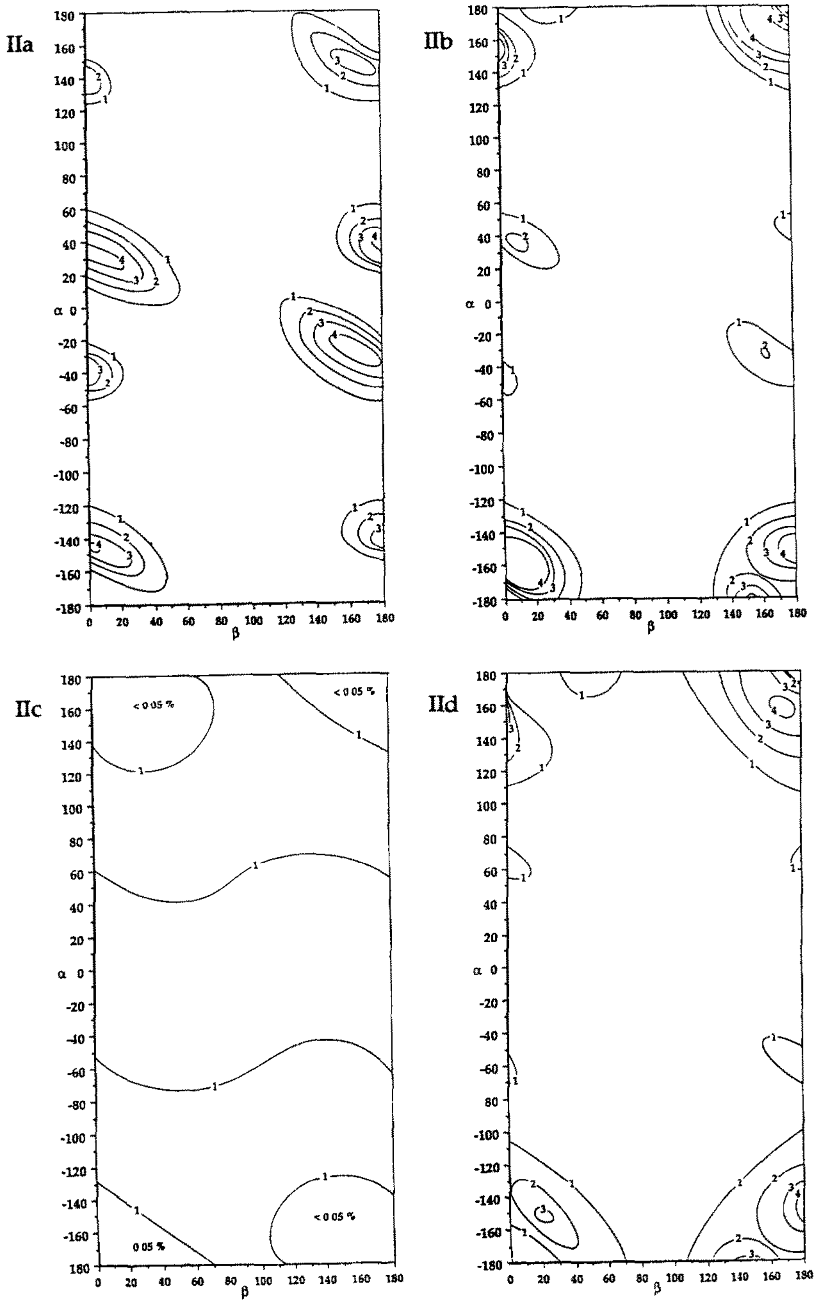
In equation (1), E_0 of a compound is the lowest energy found during the analysis In Figure II the probability ($P_i(\alpha, \beta)$) of each conformation is plotted against the torsion angles α and β for X = CO, O, CH_2 and NH, respectively

Figure II shows that all four molecules have a different probability partition The probability partitions for the compounds with X = CO, O and NH show great similarities All three structures have a high probability for conformers with an almost flat geometry, with the acetylene group pointing away from the pyrimidine (i e in the area $120° < \alpha < 180°$, $-180° < \alpha < -120°$ and $120° < \beta < 180°$, $0° < \beta < 60°$) The molecules are inclined to be flat, because this maximizes the π-electron overlap between the aromatic rings through the X group In the completely flat structure with the acetylene group pointing away from the pyrimidine ring system, ($\alpha = 180°$, $\beta = 0°$ or $180°$), there is some steric hindrance between H13 and N1 or N3, therefore, the preferred conformations are those in which the rings are somewhat twisted Another region with a relatively high probability is found for conformations with the acetylene group pointing towards the pyrimidine ring (i e in the area $20° < \alpha < 60°$, $-20° < \alpha < -60°$ and $0° < \beta < 40°$, $120° < \beta < 180°$) In these (reactive) conformations, the molecules also tend to maximize the π-electron overlap but are twisted from planarity, due to steric hindrance between the acetylene group and the pyrimidine group For X = CO, there will be steric interactions between the lone pairs of the oxygen of the carbonyl group and the acetylene in the open conformers, with the acetylene pointing away from the pyrimidine The importance of these conformations decreases for X = CO > O > NH As is seen from the Figures IIa, IIb and IId, the importance of these reactive conformations decreases in the order X = CO > O > NH

In Figure IIc it is seen that the probability partition shows a completely different pattern when X = CH_2 Since there is no π-electron overlap possible between the two aromatic rings, any conformation, which is not sterically hindered, has an almost equal probability, so there is no clear preference for any conformation of the molecule

From examining Figure II, it is obvious that the probability of molecules with conformations with a flat geometry is the highest for X = NH, as compared to the other systems

<u>Figure II</u> Probability partitions of the configurations of compounds **1B** related to the dihedral angles α and β
IIa: X = CO, IIb X = O, IIc X = CH_2, IId: X = NH
$P_1(\alpha, \beta)$ 1 = 0.05%, 2 = 0.20%, 3 = 0.40%, 4 > 0.50%



This phenomenon is most likely due to the stronger mesomeric interactions between the π-systems and the NH group as compared to the other groups Therefore, the conformers with a flat geometry are more stabilized when X = NH than when X = O, CO or CH_2

It can be stated that the possibility for a reaction to occure increases, i) when the reactants (diene and dienephile) are within short distance and ii) when the probability increases that the reactants are in these positions When the distance C5 C15 is taken as a measure of the proximity of the reactants the probability (P_d(dC5 C15)) that conformers have a short distance C5 C15 can be regarded as a parameter for the reactivity The probability of conformations to have a particular distance C5 C15 can be calculated according to equation (2) In this equation an arbitrary interval of 0 2 Å was used in sorting the conformations (Figure III, -■- lines)

$$P_d(dC5\ \ C15) = \sum_{d=d-0\ 2}^{d} P_i(d) \qquad (2)$$

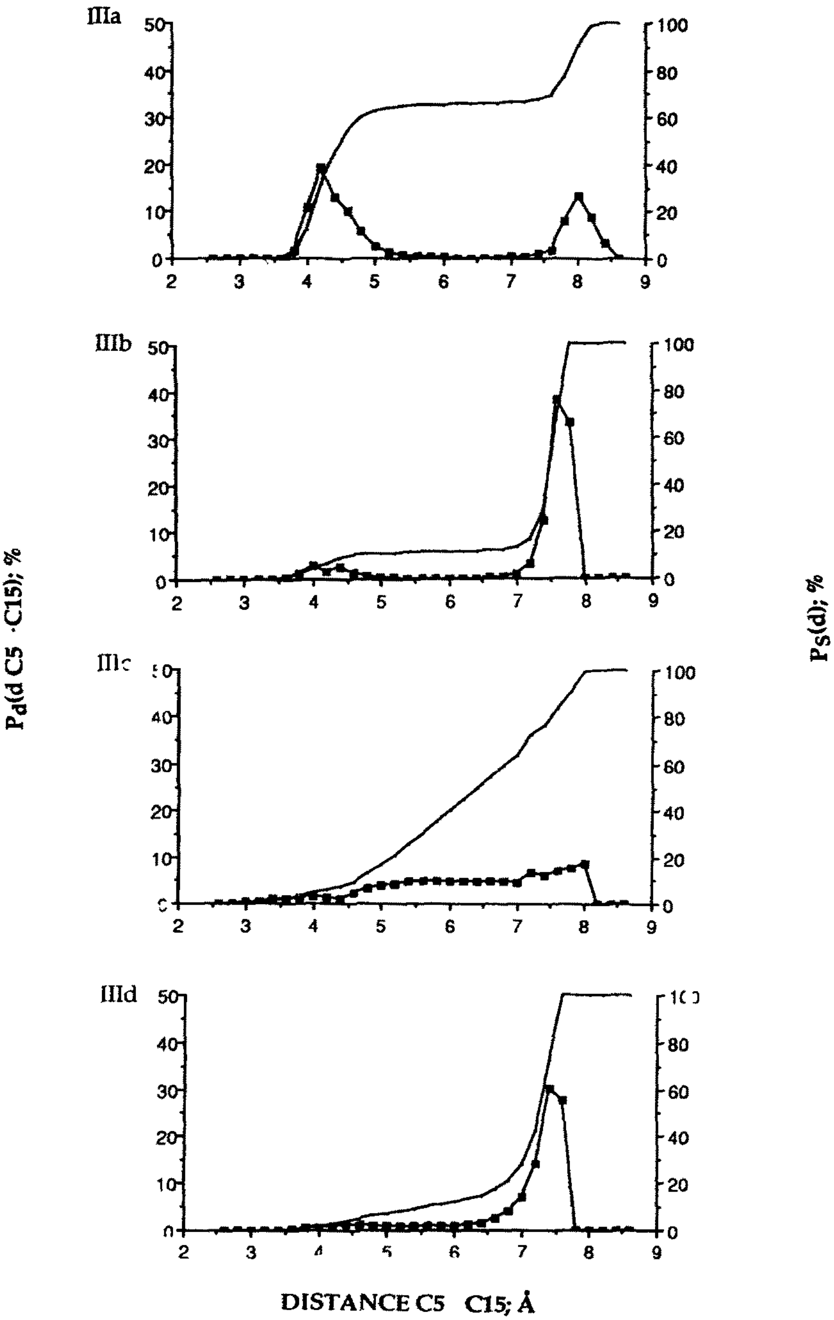
As can be seen from Figure III, the compounds with X = CO, O and NH have a preference for conformations with a distance C5 C15 of 7-8 Å (i e non-reactive conformations) and for conformations with a distance C5 C15 of about 4Å The probability of the molecules to be in conformations with a short distance C5 C15 (i e reactive conformations) increases for X = NH < O < CO For X = CH_2, there is no clear preference for a conformation with a certain distance C5 C15

The reactivity of a molecule depends on all the conformations having a short distance between the reactants To give a better insight into the reactivities, the sum of the probabilities having a distance C5 C15 shorter than a certain value d is calculated according to equation 3 The results of these calculations are plotted in Figure III (— lines)

$$P_S(d) = \sum_{d=0}^{d} P_i(dC5\ \ C15) \qquad (3)$$

The advantage of this method is that conformations which are not in an energy minimum but have a short distance between the reactants, and therefore are considered to be reactive, are also taken into account Examining the P_S(d) plots in Figure III, it can be deduced that on going from X = CO to X = O and X = NH, the summed probability of the conformations with a short distance C5 C15 decreases For X = CH_2, there is a gradual increase of the P_S(d) with an increase of the distance C5 C15 The summed probability of the molecules **1B** to have conformers with a distance between C5 C15 smaller then 4 5 Å nicely reflects the observed order of reactivity of the 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines (P_S (d) for X = CO is 25%, P_S (d) X = O is 6%, P_S (d) for X = CH_2 is 5% and P_S (d) for X = NH is 2%)

Figure III Probability partitions (P_d(dC5 C15), left hand y-axis) and summed probabilities (P_S(d), right hand y-axis) related to the distance C5 C15 of the pyrimidines **1B**
IIIa. X = CO, IIIb X = O, IIIc. X = CH_2, IIId. X = NH.
P_d(dC5 C15) ■, P_S(d): —.



Whether all conformations with a small C5 C15 distance can be regarded as being reactive, can be a matter of debate, since other aspects, like for example the angle under which the π-electron systems of the diene and dienophile approach each other, also play a role even if the heat of activation is the same Furthermore, the bond angle φ does have a slight effect on the probabilities at short distances C5 C15, although it hardly has any effect on the overall appearance of the diagrams as depicted in the Figures 2 and 3[9]

Determination of the heat of activation

Since the reactivity is normally not determined by conformational effects alone, but also by the heat of activation of the rate determining step, it was decided to calculate the transition-states and their potential energies for the conversion of **1B** into **2B** for the various molecules

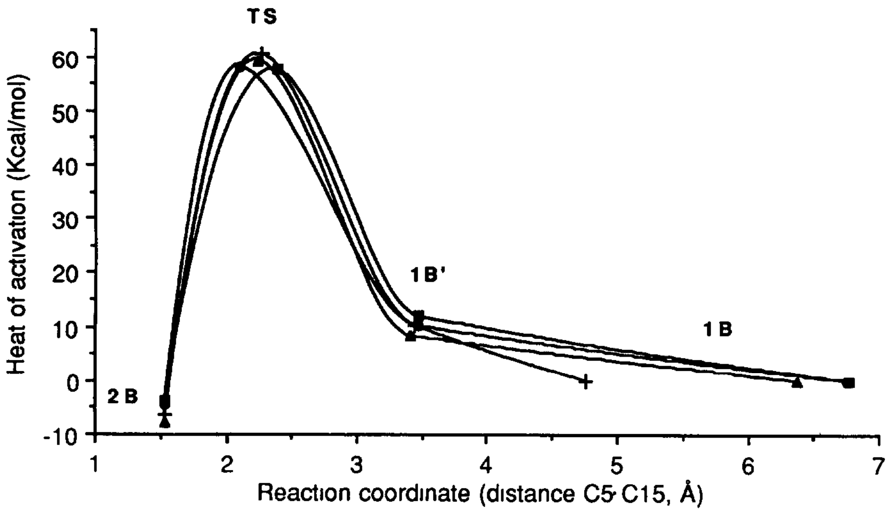
Because the cycloaddition reaction involves the interaction between the π-electron systems of diene and dienophile, it was decided to used the 'VAMP'-program[10a] This program uses the semi-empirical MNDO force field of Dewar and Thiel[10b] and the Davidon-Fletcher-Powell geometry optimization routine[11], which are generally assumed to give the most reliable results[12] for the kind of systems under study

The transition-states of the Diels-Alder reaction were determined using the saddle-point method of McIver and Komornicki[13], which was also implemented in the 'VAMP' program For reasons of computation time the saddle-point calculations were started at the conformations **1B'**[14], with a distance of 3 5 Å between C5 and C15, at which distance there was not yet any interaction between the diene and dienophile The geometry of the intermediates **2B** were determined by an unrestricted optimization of a conformation which had passed the heat of activation barrier A saddle-point calculation[13] between **1B'** and **2B** provided the transition-state geometries and their heats of formation The heats of formation of the starting conformations **1A** were determined by re-optimizing the conformations of minimal energy (E_0), as found in the conformational analyses, in the MNDO force field of the 'VAMP'-program[15]

The heats of activation of each intramolecular cycloaddition were calculated by subtracting the heats of formation of the starting point geometries from those of the transition state geometries (see Figure IV and Table III)

The calculations show that the differences in the heats of activation are rather small and that the geometries of the transtition states are rather similar as is seen in Table III, Figure IV and Figure V In fact, the differences in the heats of activation are so small that they cannot explain the pronounced differences in the observed reactivity of the 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines, nor do they reflect the observed order of reactivity The outcome of this experiment was not quite unexpected In an earlier paper[3], it was demonstrated that the influence of an electron withdrawing or donating group on the intramolecular cycloaddition of 5-(*p*-substituted phenyl)-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines was rather small This result is also in agreement with the assumption that this cycloaddition is a concerted reaction with little or no charge separation in the transition state

Figure IV Reaction profile for the inverse electron demand Diels-Alder reaction of 1B to 2B
+ X = CO, • X = O, ▲ X = CH_2, ■ X = NH



Another support for the similarity of the transition state geometries and the accessory heats of activation can be deduced from the electronic properties of the X-group When the overall electronic effect of the X-group is factorized into an inductive (σ_I) and a mesomeric (σ_M) effect[16], it is obvious that in the transition state the mesomeric effect of the X-group on the pyrimidine ring can be neglected, because of the almost perpendicular orientation of the π-systems (see Figure V) The values of σ_I of the CO, O and NH groups all have about the same magnitude (σ_{I},CO = 0 30, σ_{I},O = 0 40, σ_{I},NH = 0 30, see Table I)[16b], so it is very plausible that rather similar transition states for these three molecules are found The inductive effect of the CH_2 group (σ_{I},CH_2 = 0 04) is significantly smaller, which would result in a higher heat of activation for the cycloaddition This increase in the heat of activation however seems to be compensated by the much smaller geometrical changes in the molecule (especially the change in angle φ), when going from the starting to the transition state conformation, as compared to the other molecules (see Table III)

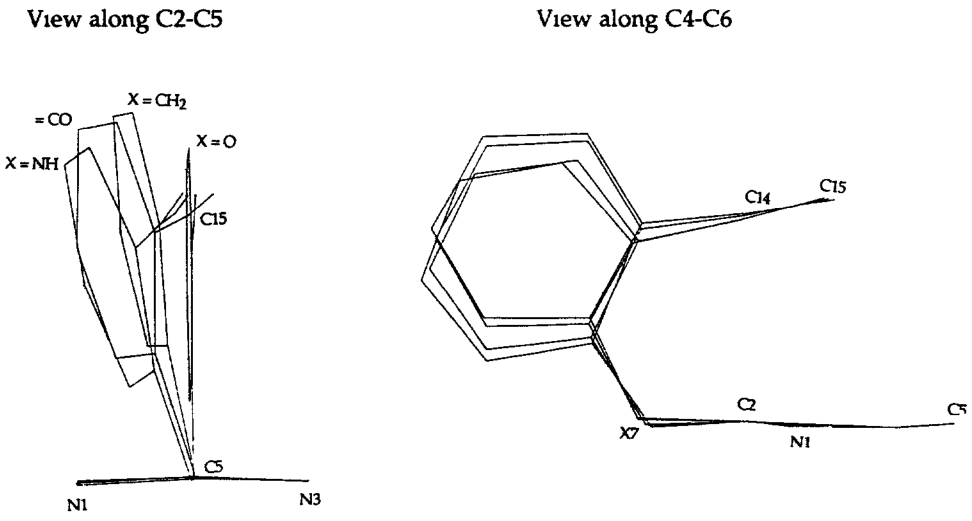
From the determination of the various transition-states and the accessory heats of activation of the rate determining Diels-Alder reaction, it is seen that these properties are almost the same for the molecules under study The small differences in the heats of activation confirms the assumption that all molecules have the same possibility to react if they are in the same reactive conformation Furthermore, the heat of activation does not reflect the observed order of reactivity for the various 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines

Table III Some important conformational parameters of the starting (**2A**), transition state (**TS**) and intermediate (**2B**) geometries, the heats of formation (H_{form}) and heats of activation (ΔH) of the conversion of **1B** to **2B**

compound	α^a	β^a	φ^a	dC2 -C14^b	dC5 C15^b	H_{form}^c	ΔH^c
CO(**1B**)	177 1	105 8	121 2	2 967	4 758	81 9	0 0
CO(**TS**)	110.9	160 6	112 7	2 151	2 263	142 4	60 5
CO(**2B**)	118 1	179 0	105 5	1 567	1 536	75 5	-6 4
O(**1B**)	99 9	178 6	123 3	3 884	6 759	77 3	0 0
O(**TS**)	95 3	178 6	111 6	1 945	2 096	135 5	58 2
O(**2B**)	119 3	179 8	108 6	1 576	1 536	72 8	-4 5
CH_2(**1B**)	93 3	84 2	113 2	3 814	6 379	109 0	0 0
CH_2(**TS**)	80 7	169 7	110 3	2 155	2 242	168 3	59 3
CH_2(**2B**)	119 5	179 1	103 7	1 570	1 532	101 2	-7 8
NH(**1B**)	157 4	160 4	124 1	3 947	6 768	116 1	0 0
NH(**TS**)	111 7	170 4	113 9	2 190	2 390	174.4	58 3
NH(**2B**)	113 9	174 5	107 2	1 570	1 533	112 1	-4 0

^{a}angles in degrees, ^{b}distances in Å, ^{c}enthalpy in Kcal/mol

Figure V Superposition of the transition state geometries of the 2-(2-ethynylphenyl-X)-pyrimidines in the conversion of **1B** to **2B**



View along C2-C5

View along C4-C6

CONCLUSIONS

From the calculations presented in this paper, it can be seen that the heat of activation of the rate determining conversion of **1B** into **2B**, does not reflect the observed order of reactivity of the pyrimidines **1A** Furthermore, the calculated differences between the transition-states (geometric and energetic) are too small to explain the differences in the observed reactivities of the compounds **1A**

The conformational analyses of the different systems however, do predict an order of reactivity that is in good agreement with the observed order of reactivity of the compounds **1A**, which seemed puzzling at the start of this investigation Especially the summed probabilities for short distances between the reacting sites ($P_S(d) < 4Å$) seem to reflect the observed order of reacivity very well From these results, it can be concluded that the conformational properties mainly determine the order of reactivity of the 2-(2-trimethylsilylethynylphenyl-X-)pyrimidines **1A** investigated in this study

ACKNOWLEDGEMENTS

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9 A variation of +5 or -5 degrees in φ resulted in slightly different p_i values for conformations with a distance C5 C15 smaller than 4 5 Å, but the probability partitions still reflected the observed order of reactivity of the pyrimidines **1A**

10 a The semi-empirical MNDO method was part of the 'VAMP' program, 'VAMP' - Erlangen vectorized Molecular Orbital Package, Version 4 10 (based on AMPAC 1 0 and MOPAC 4 0) b The MNDO calculations were all carried out on a CONVEX C120 computer Original reference on MNDO M J S Dewar and W Thiel, *J Am Chem Soc*, **1977**, *99*, 4899

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14 The geometry of the conformations **1A'** were determined using the common reaction-coordinate method, starting with the MNDO re-optimized geometries of **1A** To bring the reaction centers together with as little restrictions to the geometry as possible, dummy atoms were centered between the diene system (C2-C5) and the dienophile system (C14-C15) and brought together with an increment of 0 5 Å As the reaction coordinate, the distance C5 C15 was monitored

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15 Due to the different nature of the semi-empirical and molecular mechanics methods it is evident that the MNDO re-optimized conformations of minimal energy (Table III) are slightly different from to the original MM optimized conformations of minimal energy (Table II)

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