

COMPUTATIONAL STUDIES TOWARDS THE SELECTIVITY AND REACTIVITY OF 5-PROPYNYLOXYCYCLOALKANEPYRIMIDINES IN INTRAMOLECULAR DIELS-ALDER REACTIONS.

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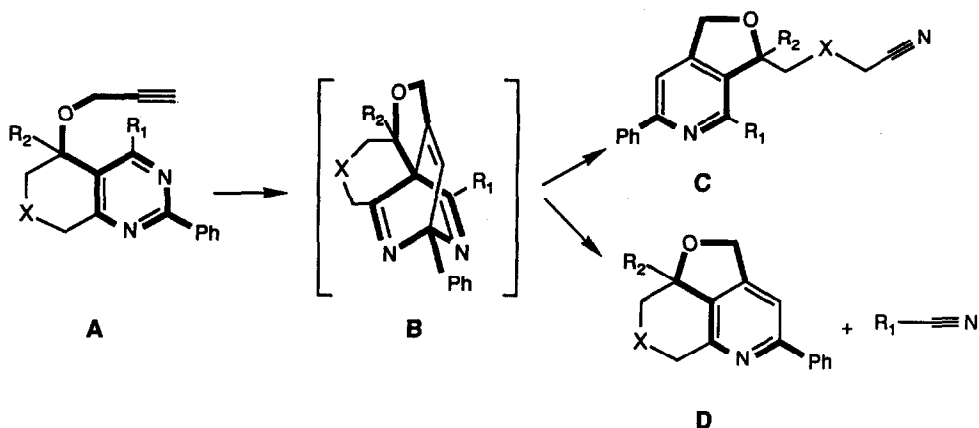
Key Words: Intramolecular Diels-Alder reactions; Selectivity; Reactivity;
MNDO/PM3 and MMX calculations.

Abstract: Computational studies (MNDO/PM3 and MMX) were performed towards the selectivity and reactivity of the ringtransformation reactions of the 5-(1-propynyloxyethyl)pyrimidine derivatives **A1-8**. Determination of the energy and dipole moments of the transition states of the different possible reaction pathways revealed that the ratio of the product formation was determined by the polarity of the transition states, as expressed by their dipole moments, in combination with the dipole moment of the reaction medium. Also the reactivity of the compounds under study appeared to depend on the polarity of the transition state of the initial Diels-Alder reaction. The differences in dipole moments of the different TS's are ascribed to the geometry of the molecules in the TS's. Furthermore, a comparison of the heats of activation of the initial Diels-Alder reaction and the subsequent retro Diels-Alder reaction showed that the first one is the rate determining step.

INTRODUCTION

In our series of publications about intramolecular Diels-Alder reactions of pyrimidines¹, we reported in a preceding paper² on the synthesis of the 2-phenyl-5-(1-propynyloxyethyl)-pyrimidine derivatives **A** (Scheme 1). Heating of these compounds in nitrobenzene at 140°C yields, in principle, the annelated pyridine derivatives **C** and **D** by expulsion of X-CH₂-CN or R₁-CN respectively, from the hypothetical intermediate **B**. However, a remarkable selectivity in the product formation was observed depending on the size of the cycloalkane ring (Table I).

Furthermore, the reactivity of the compounds under study was found to be increased 4 - 10 times upon introduction of a methyl group at C5³ (Table I).



X = -CH₂-, R₁ = H, R₂ = H (1)

X = -CH₂-, R₁ = H, R₂ = Me (2)

X = -CH₂-, R₁ = Me, R₂ = H (3)

X = -CH₂-, R₁ = Me, R₂ = Me (4)

X = -CH₂CH₂-, R₁ = H, R₂ = H (5)

X = -CH₂CH₂-, R₁ = H, R₂ = Me (6)

X = -H H-, R₁ = H, R₂ = H (7)

X = -H H-, R₁ = H, R₂ = Me (8)

Scheme 1: Reaction scheme for the ringtransformation of the pyrimidines A.

Table I: Yields and reaction rates ($t_{1/2}$) for the ringtransformation of the compounds A into the annelated pyridines C and/or D (nitrobenzene at 140 °C) (for formulas see Scheme 1).

Starting material A	Reaction Rate $t_{1/2}^{a, b}$	Products			
		C	yield ^c	D	yield ^c
1	5.08	1	47	1	33
2	0.81	2	83	2	.d
3	3.22	3	79	3	5
4	3.08	4	89	4	.d
5	7.95	5	.d	5	83
6	0.71	6	.d	6	92
7	17.45	7	.d	7	77 ^e
8	4.50	8	.d	8	81 ^e

^a $t_{1/2}$ in hours, ^bThe reactions were assumed completed and worked up after 8 times $t_{1/2}$, ^c% isolated yields. ^dNo product detected. ^ePartially isolated as oxidized material⁴.

To gain more insight into the Diels-Alder behaviour of the studied compounds we performed computational studies towards the observed selectivity and reactivity of the ringtransformations of compounds A. To limit the computation time the phenyl substituent at position 2 of the compounds under study were replaced by a hydrogen atom. It is assumed that this replacement does not influence the essential properties of the compounds under study. In the computational studies a combination of Molecular Mechanics and semi-empirical methods were used .

Selectivity of the retro Diels-Alder reaction

The selectivity of the ringtransformation reaction is determined in the retro Diels-Alder reaction of intermediate B (Figure 1). This unstable molecule is formed in the first step in the Diels-Alder reaction and immediately disproportionates yielding C and/or D (Scheme 1). Because it was never possible to isolate or detect the intermediate B, it is believed that the retro Diels-Alder reaction is much faster than the initial intramolecular Diels-Alder reaction. Therefore, the conversion of A into B is supposed to be the rate determining step in the reaction sequence of A to C and/or D. From Table I it can be seen that the presence of a cyclohexane ring in the compounds A1-4 favours the formation of C, whereas the presence of a cycloheptane ring (A5-6), or no ring at all (A7-8), favours the formation of D. As these differences in the geometry of the molecules do not affect their electronic properties it seems justified to assume that the selectivity of the ringtransformation depends on sterical properties. In order to investigate whether there is a correlation between the structure of B and the observed selectivity its geometric and electronic properties were computed.

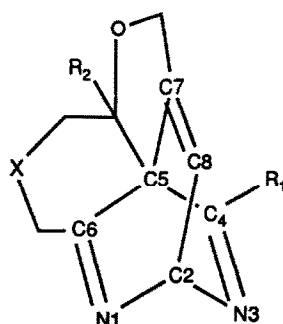


Figure 1: The hypothetical intermediate B.

The geometry of B was determined with the Molecular Mechanics adapted MMX⁵ program and also with the semi-empirical VAMP program^{6,7} using the MNDO/PM3 hamiltonian (Table II). From Table II can be seen that there is no clear correlation between the rate of product formation and the length of the bonds to be broken. An increase of the bond lengths between

the fragment to be extruded and the part of the molecule which will form the new aromatic system could not be found. Also the assumption that the breaking of bonds is not a concerted process and that only one of the bonds between the leaving part and the rest of the molecule is correlated with the observed selectivity cannot be confirmed by the data in Table II⁸.

Table II: Most important bond lengths in the intermediates **B** (Figure 1) as calculated with the semi-empirical VAMP program and the Molecular Mechanics adapted MMX program. The bonds found to be broken in the retro Diels-Alder reaction are underlined

B	d(C2-N1) ^a		d(C2-N3) ^a		d(C2-C8) ^a		d(C5-C6) ^a		d(C5-C4) ^a		d(C5-C7) ^a	
	MMX	VAMP	MMX	VAMP	MMX	VAMP	MMX	VAMP	MMX	VAMP	MMX	VAMP
1	<u>1.497</u>	<u>1.505</u>	1.497	1.510	1.515	1.525	<u>1.506</u>	<u>1.528</u>	1.508	1.528	1.500	1.525
2	<u>1.495</u>	<u>1.503</u>	1.493	1.510	1.513	1.525	<u>1.511</u>	<u>1.531</u>	1.511	1.529	1.503	1.524
3	<u>1.501</u>	<u>1.504</u>	1.518	1.505	1.516	1.524	<u>1.492</u>	<u>1.531</u>	1.505	1.536	1.497	1.526
4	<u>1.498</u>	<u>1.500</u>	1.518	1.498	1.516	1.520	<u>1.491</u>	<u>1.539</u>	1.510	1.545	1.495	1.530
5	1.492	1.501	<u>1.501</u>	<u>1.511</u>	1.510	1.522	1.510	1.533	<u>1.512</u>	<u>1.533</u>	1.505	1.526
6	1.490	1.498	<u>1.499</u>	<u>1.510</u>	1.509	1.521	1.513	1.536	<u>1.508</u>	<u>1.535</u>	1.515	1.527
7	1.491	1.497	<u>1.499</u>	<u>1.509</u>	1.510	1.521	1.515	1.538	<u>1.514</u>	<u>1.534</u>	1.507	1.528
8	1.495	1.495	<u>1.499</u>	<u>1.500</u>	1.509	1.529	1.520	1.548	<u>1.513</u>	<u>1.542</u>	1.511	1.540

^ain Å.

In a further attempt to understand the origin of the selectivity in the retro Diels-Alder reaction it was decided to determine the energy of the transition states (TS) of the two possible fragmentation reactions yielding **C** and **D**, respectively. By means of the SADDLE option⁹ in the VAMP program the TS's for both retro Diels-Alder reactions were determined roughly. For a more accurate determination of the energy of the TS's, the heats of formation and the electronic properties were refined using the Non-Linear Least Square gradient minimisation routine (Table III).

From Table III it can be concluded that the heats of formation of the two possible TS's do not consequently reflect the observed ratio of the products (Table I). For the compounds 5-8 an energy difference of 3 - 4 kcal between the two possible TS's agrees with the observed selectivity of the cycloreversion reaction. However, for the compounds 1-4 the calculated energy difference between the TS's is relatively small (1 - 2 kcal) and predicts preference for the formation of **D**, which does not agree with the observations. However, one of the limitations of the applied semi-empirical methodology is that they are parameterized for systems in vacuum, which implies that the calculations are only applicable to systems that do not have strong interactions with their surrounding. Apparently the use of the strong polar nitrobenzene as a reaction

medium is of influence on the retro Diels-Alder reaction which determines the selectivity of the ringtransformation. To investigate whether there may be any interaction between the reaction medium and the TS's of the cycloreversion reactions the polarity of the TS's yielding the products C and D were determined by calculation of the dipole moments. From Table III it is seen that the dipole moment of the $TS_{B \rightarrow C}$ is significant higher than the dipole moment of $TS_{B \rightarrow D}$. These differences in dipole moments (D) may possibly explain the selectivity of the retro Diels-Alder reaction.

Table III: Heats of formation (H_f) of B, $TS_{B \rightarrow C}$, $TS_{B \rightarrow D}$, C and D and the heats of activation (H_{act}) and the dipole moments (D) for both TS's. The data for the preferred reaction path are underlined.

	B	$TS_{B \rightarrow C}$			$TS_{B \rightarrow D}$			C	D
		H_f^a	H_f^a	D^b	H_{act}^a	H_f^a	D^b		
1	27.68	<u>67.51</u>	<u>2.700</u>	<u>39.83</u>	65.97	1.834	38.29	<u>15.75</u>	23.30
2	23.48	<u>62.26</u>	<u>2.730</u>	<u>38.78</u>	59.98	2.082	36.50	<u>10.24</u>	18.72
3	18.73	<u>57.90</u>	<u>2.641</u>	<u>39.17</u>	56.07	2.046	37.34	<u>9.99</u>	12.87
4	17.81	<u>56.50</u>	<u>2.600</u>	<u>38.69</u>	55.21	2.221	37.40	<u>1.71</u>	4.85
5	28.28	66.45	2.069	38.17	<u>63.72</u>	<u>1.914</u>	<u>35.44</u>	10.01	<u>16.75</u>
6	24.85	61.63	2.081	36.78	<u>58.38</u>	<u>2.011</u>	<u>33.53</u>	6.47	<u>9.36</u>
7	27.48	64.13	2.301	36.65	<u>61.04</u>	<u>1.913</u>	<u>33.56</u>	13.28	<u>1.24</u>
8	24.73	59.37	2.413	34.64	<u>54.97</u>	<u>2.037</u>	<u>30.24</u>	7.72	<u>3.88</u>

^ain kcal/mol. ^bin Debye.

Although the stabilization of a Diels-Alder TS by a polar solvent is relatively small as compared to e.g. substitution reactions, there are several reports on rate enhancements by increasing the polarity of the reaction medium¹⁰. Recently, Blake *et al*¹¹ reported a stabilization of the TS of the Diels-Alder reaction of methyl vinyl ketone with cyclopentadiene of -4.2 kcal in water ($D = 1.85$ Debye) and -2.4 kcal in methanol ($D = 1.70$ Debye) as compared to the reaction in propane ($D = 0.08$ Debye)¹². On account of these observations we propose that the large dipole moment of nitrobenzene ($D = 4.22$ Debye) may possibly be of influence on the TS's of the different reaction pathways. As can be seen from Table III the relative differences in dipole moments between $TS_{B \rightarrow C}$ and $TS_{B \rightarrow D}$ are about 0.4 - 0.6 Debye in the compounds 1-4 and about 0 - 0.3 Debye for the compounds 5-6. These large differences in polarity reflect different stabilization energies for the different TS's. If we assume an additional stabilization of -2 - -4 kcal for a

relative difference in dipole moment of 0.5 Debye, the readjusted values of the heats of activation do agree with the observed selectivity in the retro Diels-Alder reaction (Table III).

To investigate the origin of the large differences in the dipole moments of $TS_{B \rightarrow C}$ and $TS_{B \rightarrow D}$ we determined the geometries of the two possible TS's (Figure 2). Because the molecular dipole moment equals the vector sum of the individual bond moments it is obvious that a TS with a non concerted character gives rise to a larger dipole moment than a TS of a concerted reaction. As a measure for the concertedness of the TS's we determined the difference in bond lengths of the bonds to be broken in the cycloreversion reactions (Table IV).

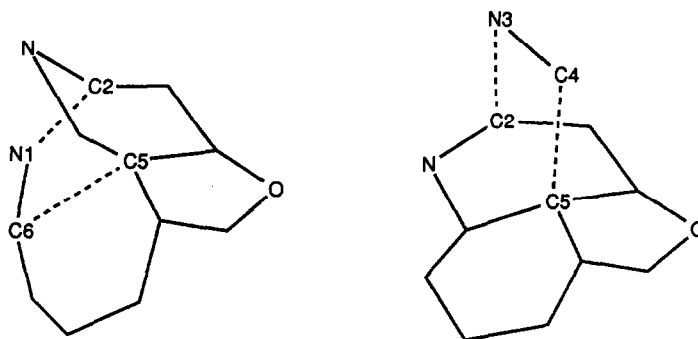


Figure 2: $TS_{B \rightarrow C}$ and $TS_{B \rightarrow D}$ for the retro Diels-Alder reaction of compound 1.

Table IV: Differences in bondlengths (Δd) in the $TS_{B \rightarrow C}$ and $TS_{B \rightarrow D}$ of the bonds to be broken in the cycloreversion reactions (Figure 2).

$$\Delta d \text{ } TS_{B \rightarrow C} = dC2-N1 - dC5-C6; \Delta d \text{ } TS_{B \rightarrow D} = dC2-N3 - dC5-C4$$

Compound	$\Delta d \text{ } TS_{B \rightarrow C}^a$	$\Delta d \text{ } TS_{B \rightarrow D}^a$	Compound	$\Delta d \text{ } TS_{B \rightarrow C}^a$	$\Delta d \text{ } TS_{B \rightarrow D}^a$
1	-0.262	-0.121	5	-0.363	-0.266
2	-0.263	-0.154	6	-0.385	-0.271
3	-0.333	-0.243	7	-0.418	-0.216
4	-0.301	-0.258	8	-0.447	-0.300

^ain Å.

From Table IV and III it can be seen that the larger dipole moment of the $TS_{B \rightarrow C}$ (Table III) corresponds with a larger difference in the bonds to be broken in the retro Diels-Alder reaction. Investigation of the geometries of the TS's makes it plausible that the non concerted character of the $TS_{B \rightarrow C}$ may be explained by the strain effect of the cycloalkane ring in the compounds 1-6 or by the steric interactions between the methyl groups at C6 and C5 in the compounds 7-8.

Reaction rate of the Diels-Alder reaction

It was stated before, that the rate of the ringtransformation reaction is determined in the initial Diels-Alder step yielding intermediate B. From Table I it can be seen that replacement of hydrogen at C5 by a methyl group gives rise to rate increasement of 4 - 10 times. However, it seems unlikely that this is caused by a change in the HOMO/LUMO energy separation, because R₂ is not directly attached to the diene or dienophile part of the molecule. Therefore, the contribution of the inductive effect of the methyl group cannot be an important factor to the observed rate enhancement. To confirm this, the HOMO and LUMO energies of the diene and dienophile parts of the compounds A were determined with the semi-empirical VAMP program⁶, using the MNDO-PM3 Hamiltonian after geometry optimization⁷ (Table V). As can be seen from Table V the introduction of a methyl group at C5 only slightly influences the HOMO/LUMO energy separation in the of the compounds A. Comparing the compounds 1 and 2, the introduction of the methyl group decreases the energy difference between the frontier orbitals of the diene and the dienophile (HOMO_{dp} - LUMO_{de}) with 0.088 eV. This effect of the methyl group does not seems large enough to account for the observed enhanced reactivity of the methyl substituted compounds.

From the calculation of the HOMO and LUMO energy levels, it is clear that all Diels-Alder reactions studied in this paper can be classified as inverse¹³, although the electron donating effect of the methyl group at C4 in the compounds 3 and 4 slightly changes the character of the Diels-Alder reaction into the direction of a neutral type.

Table V: Energy differences between the Frontier Orbitals of the diene and the dienophile moieties of the compounds A.

$$\Delta E_{\text{norm.}} = E_{\text{HOMO(diene)}} - E_{\text{LUMO(dienophile)}}; \Delta E_{\text{inv.}} = E_{\text{HOMO(dienophile)}} - E_{\text{LUMO(diene)}}$$

A	$\Delta E_{\text{norm.}}^a$	$\Delta E_{\text{inv.}}^a$	A	$\Delta E_{\text{norm.}}^a$	$\Delta E_{\text{inv.}}^a$
1	11.605	10.208	5	11.800	10.229
2	11.769	10.120	6	11.663	10.195
3	11.336	10.844	7	11.717	10.164
4	11.799	10.799	8	11.825	10.151

in eV.

On account of the calculated energy differences between the HOMO's and LUMO's of the different compounds it is not plausible to expect large differences in the heats of activation of the initial Diels-Alder reaction. However, in order to estimate the influence of the solvent on the reactivity the heats of formation and the dipole moments of the TS's were determined. The heats of activation (H_{act}) of the Diels-Alder reactions were calculated by subtracting the heats of

formation of the TS's from the heats of formation of the lowest energy conformation of compounds **A** (Table VI). From Table VI it is clear that neither the differences in the heats of activation nor the magnitude of the energy difference correlate with the observed rate enhancements upon introduction of a methyl group at C5. However, the calculations show that introduction of the methyl group enhances the dipole moments of the TS's. Therefore, a stabilization of the TS's having larger dipole moments by the polar nitrobenzene has to be taken into account. Applying the same stabilization factor of -2 - 4 kcal (see above) for a relative difference in dipole moment of 0.5 Debye, leads to heats of activation, that do reflect the observed rates of reaction (Table I). The polarity of the TS's appears to be an important factor for explaining the observed reactivity of the initial Diels-Alder reactions.

Table VI: Heats of formation (H_f) of the starting compounds **A** and the dipole moments (D) and heat of activation (H_{act}) of the $TS_{A \rightarrow B}$.

	$TS_{A \rightarrow B}$					$TS_{A \rightarrow B}$			
	A	H_f^a	H_f^a	D^b		H_{act}^a	A	H_f^a	H_f^a
1	37.36	79.14	1.910	41.78	5	37.75	79.55	2.045	41.80
2	35.98	77.89	2.719	41.91	6	32.83	72.44	2.431	39.61
3	32.83	72.90	2.008	40.07	7	36.59	76.45	1.899	39.86
4	29.21	69.92	2.414	40.71	8	35.27	75.51	2.152	40.24

^ain kcal/mol. ^bin Debye.

Tables III and VI show that the heats of activation of the initial Diels-Alder reaction (Table VI) are about 3-5 kcal higher than those of the retro Diels-Alder reaction (Table III). Even after a correction for the differences in dipole moments in the respective TS's, the heats of activation of the initial Diels-Alder reactions are still higher. This is in good agreement with our assumption that the rate of the ringtransformation reactions is determined by the initial Diels-Alder reaction.

CONCLUSIONS

The observed selectivity and reactivity of the ringtransformation reaction of 5-(1-propynyloxyethyl)pyrimidine derivatives **A1-8** appears to be determined by the differences in polarity of the respective TS's, stabilized by the large dipole moment of the reaction medium (nitrobenzene). An assumed stabilization of approximately -2 - 4 kcal for a relative difference in dipole moments of 0.5 Debye brings the experimental data and calculations in good agreement. The differences in the dipole moments are probably due to the more or less concerted character of the Diels-Alder reactions. Furthermore, a comparison of the heats of activation of the initial

addition step and the subsequent retro reaction shows that the initial step is rate determining, because the heat of activation of the retro reaction is 3-5 kcal lower in energy.

EXPERIMENTAL SECTION

The computational methods used in this paper have been described in previous publications of our group¹⁴.

All Molecular Mechanics calculations were performed on the VAX cluster of the CAOS/CAMM Centre, University of Nijmegen, The Netherlands. The semi-empirical VAMP program was used on the CONVEX C120 computer of the CAOS/CAMM Centre.

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- 3 The reaction rates of the different compounds were determined, by careful integration of the signals in the ¹H-NMR spectra between 4.5 and 6.5 ppm, comparing the amounts of the starting material and the products C and/or D, at appropriate time intervals.
- 4 The compounds D7 and D8 appeared to oxidize rapidly during their isolation yielding 1,3-dihydro-6-phenylfuro[3,4-c]pyridine-1(3H)-ones. Similar observations were reported in reference 1b.
- 5 The MMX program is derived from MM2 (QCPE 395) with MMP1 π subroutines (QCPE 318) incorporated for delocalized π electrons.

- 6 The 'VAMP' program ('VAMP' - Erlangen Vectorized Molecular Orbital Package, Version 4.10) is based on AMPAC 1.0 and MOPAC 4.0.
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