QUANTUM-CHEMICAL INSIGHT INTO MECHANISM OF COMBINED INTRA-INTERMOLECULAR CYCLOADDITION

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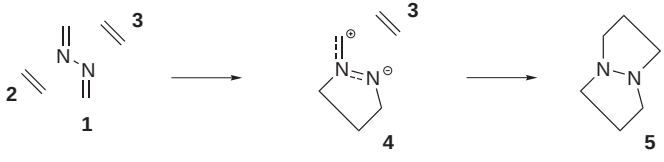
Dedicated to Professor Rudolf Zahradník on the occasion of his 75th birthday.

Two different reaction mechanisms of a mixed criss-cross cycloaddition with opposite sequence of reaction steps, intra-intermolecular and inter-intramolecular, were explored by quantum-chemical calculations at the MP2 and B3LYP levels of theory and with cc-pVDZ basis set. It was found that the rate-determining step in the both mechanisms is the first step regardless of the mechanism. The Gibbs activation barrier of the intramolecular step of the intra-intermolecular sequence is by 10.4 kcal mol^{-1} lower than that of the intermolecular step of the inter-intramolecular sequence at the MP2 level of theory and almost the same at the B3LYP level of theory. This together with known experimental data confirms that the intra-intermolecular sequence is the most probable mechanism.
Keywords: Cris-cross cycloadditions; Density functional theory; Molecular modeling.

Criss-cross cycloaddition (CCC) reactions have been known for a long time. The first such reactions were carried out in 1917 (ref.[1]). These were interactions of various azines with heterocumulenes or with their precursors namely phenyl isocyanate or with *in situ* generated cyanic or thiocyanic acid. Later, it was shown that criss-cross cycloadditions consist of two consecutive 1,3-dipolar cycloadditions[2]. General scheme referring to CCC in intermolecular layout is depicted in Scheme 1.

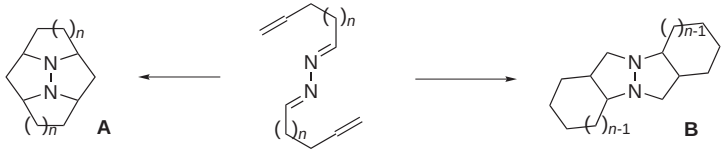


SCHEME 1

The reaction of azine **1** with dipolarophile **2** leads to 1:1 cycloadduct **4**, which immediately reacts with the second dipolarophile **3** to form the final criss-cross cycloaduct **5**. Other heterodienes such as 1,4-diazabuta-1,3-dienes[3] or, in special conditions, precursors of 1,2-diazabuta-1,3-dienes[4] are also often used. These heterodienes only occasionally undergo competitive Diels–Alder cycloadditions due to strong preference of *s-trans* conformation and different electronic constitution[5].

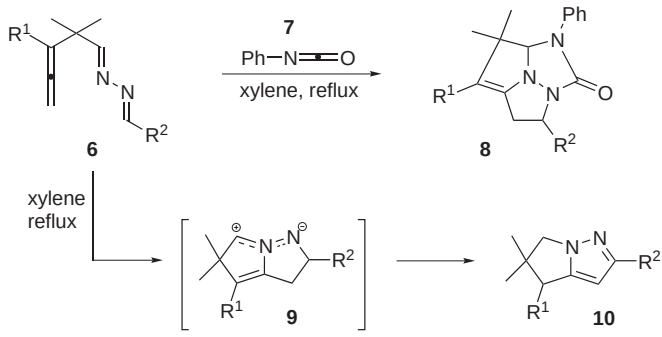
Use of different dipolarophiles, such as **2** and **3**, can extend the basic scheme of CCCs. In general, there are two different ways to do it. The first one is based on isolation of 1:1 cycloadduct **4** that will react with another dipolarophile **3** in the subsequent reaction step[2]. The method was used for preparation of many mixed intermolecular criss-cross cycloadducts, but this is limited only to a special type of reacting compounds, **1** and **2**, which enable successful isolation of 1:1 cycloadduct **4**. Another way of preparing mixed intermolecular CC cycloadducts is based on different reactivity of the two dipolarophiles, **2** and **3**, that react with heterodiene **1** in one-pot reaction[6]. However, not only mixed intermolecular CC cycloadducts are products of this reaction type, also symmetrical intermolecular cycloadducts are formed.

If both dipolarophiles, **2** and **3**, are parts of a heterodiene **1**, then intramolecular CC cycloadducts are formed (Scheme 2). Regioselectivity of 1,3-dipolar cycloadditions, the length *n* of the side chains between dipolarophiles and the heterodiene, and the thermodynamic stability are probably driving forces which distinguish between the two possible cycloadducts with central[7] **A** and lateral[8,9] **B** ring fusion.



SCHEME 2

Recently, we successfully combined the inter- and intramolecular type of CCC [10] (Scheme 3). In this reaction, nonsymmetrical azine **6** containing only one dipolarophile in molecule reacts with phenyl isocyanate **7** to form mixed intra-intermolecular criss-cross cycloadduct **8**. Product **8** is a very interesting compound because the system composed of three fused five-membered rings is prepared in one-pot reaction in a relatively high yield.



R^1 = CH_3, CH_3CH_2; R^2 = 4-methoxyphenyl

SCHEME 3

Mixed intra-intermolecular CCC can take place *via* two different mechanisms. In the first one, the intramolecular reaction within azine **6** would precede the intermolecular reaction of the 1:1 cycloadduct with phenyl isocyanate. In the second mechanism, the sequence of both 1,3-dipolar cycloadditions would be opposite. We assume that the intramolecular cycloaddition followed by the intermolecular one is the more probable alternative. The assumption is based on several experimental observations. First, none symmetrical (inter-inter) criss-cross cycloadduct was found in the crude reaction mixture. Second, heating of azine **6** without phenyl isocyanate leads to compound **10** in a reaction time comparable to CCC. Compound **10** is probably a rearranged 1:1 cycloadduct **9**. These two experimental observations imply that the rate of the intramolecular step is higher or equal to the rate of the intermolecular one.

Only detailed kinetic studies can give ultimate solution of the mechanism. Unfortunately, this would be a very time-consuming procedure. Therefore, we have employed quantum-chemical methods to gain a better insight into the mechanism. In this paper, we present calculations of energies along possible pathways, intra-inter and inter-intra. Because of the complexity and the size of the studied system, we have used some restrictions. Calculations were done on a simplified model in which all side groups (methyl, phenyl, *etc.*) are replaced by hydrogen atoms with the exception of phenyl isocyanate. This species was replaced with methyl isocyanate.

COMPUTATIONAL DETAILS

All calculation presented here were performed using the Gaussian 98 (G98) suite of programs[11]. Final geometries along both pathways were optimized with the density functional theory (DFT) employing the hybrid B3LYP functional (using Becke's three-parameter exchange functional[12] and the correlation functional of Lee, Yang, and Parr[13,14]) with the cc-pVDZ basis sets. This optimization was also performed using the Møller–Plesset theory truncated at the second order MP2, using the same basis set. Minima were found using standard optimization techniques and first-order transition states were found using the Berny transition-state optimization algorithm with the explicitly calculated Hessian in the first optimization step. The nature of all stationary points was determined by vibrational analysis using the same method and basis set. All minima presented in this study have all real vibrational frequencies and the first-order transition states have only one imaginary vibrational frequency.

Structures that were used for final calculations were found with the B3LYP functional using a smaller basis set (6-31G*). Tentative structures for this calculation level were found in all cases by a coordinate driving. The driving was performed by relaxed potential energy surface scan implemented in G98.

The thermodynamic functions such as the enthalpy and Gibbs energy were calculated for the system as ideal gas at temperature 413 K (≈140 °C) and pressure 101 325 Pa. The zero-point vibrational energies used for their calculations were scaled by a standard value. Although our model system contains one methyl group, the calculated thermo chemical energies are not corrected for these possible low-energy barrier internal rotors, as we do not expect they will make a substantial contribution to final results.

RESULTS AND DISCUSSION

The key point for a study of a reaction mechanism using quantum-chemistry tools is location of stationary points on the potential energy surface (PES). In our case, this includes searching for transition states of 1,3-dipolar cycloadditions and for further energy minima that characterize reactants and products of such cycloadditions. Two bonds are formed in 1,3-dipolar cycloaddition. This process can proceed simultaneously (concerted mechanism) or in two consecutive steps (stepwise mechanism). The stationary points on PES were located by the coordinate driving method. This method enables a stepwise change of a defined internal coordinate while other coordinates are fully optimized to the energy minimum. Since

the driving implementation in G98 makes it possible to change only one coordinate at a time, the driving method cannot be simply applied in the reactant-to-products direction due to a very high flexibility of the reactants. Therefore, the driving was performed in the opposite direction.

The initial structure for all the drivings was the final product of the mixed intra-intermolecular CCC. This structure was prepared from scratch and subsequently optimized at the molecular-mechanics, semiempirical (PM3) and B3LYP/6-31G* levels. During the driving, one of the formed bonds in the product was stepwise elongated, which leads to an energy increase. If the explored 1,3-dipolar cycloaddition proceeds by the concerted mechanism, the system reaches the energy maximum and in the next step of driving, the energy drops rapidly down as the second bond is spontaneously broken. On the other hand, in the stepwise mechanism, the energy slowly decreases after energy maximum is reached. The geometries with maximum energy obtained by the above driving were then considered to be tentative transition states and they were fully optimized to a first-order transition state with the explicitly calculated Hessian at the first optimization point. The minima found by the above driving were considered to be reactants and were fully optimized. In the case of the stepwise mechanism, however, two drivings were performed with subsequent elongation of the first and then the second bond. The minimum found by the first driving is an ionic intermediate of such stepwise dipolar cycloaddition.

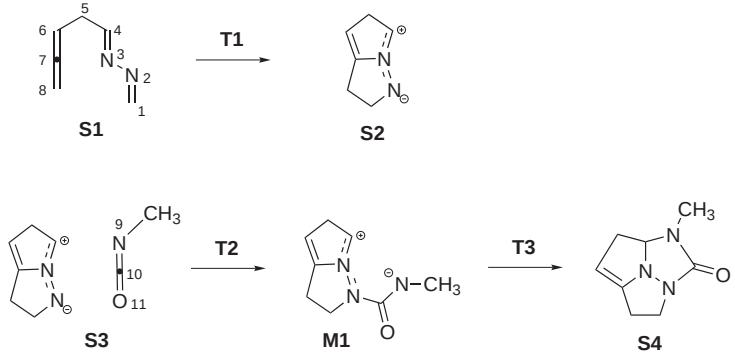
All stationary points found were then recalculated at a higher level of theory and with a larger basis set, namely MP2/cc-pVDZ and B3LYP/cc-pVDZ. Also thermodynamic parameters were calculated at both the above levels at temperature 413 K (boiling xylene) and normal pressure. These calculations are limited to the systems that behave as ideal gases, which is not our case. Nevertheless, the used solvent is not polar and the reactant concentrations in the reaction mixture are small. Therefore, we believe that the error in calculated thermodynamic energies is the same for all structures and vanishes when relative energy values are considered.

In the next two sections, the results of coordinate driving for both possible pathways are discussed. The data are presented in the opposite order than they were calculated.

Intra-Intermolecular Sequence

According to the procedure described above, it was found that the first intramolecular step leading from structure **S1** to 1,3-dipolar structure **S2** is concerted (Scheme 4, Fig. 1). However, the next step, which is inter-

molecular and leads from structure **S3** to the final CC cycloadduct **S4**, is not concerted in this particular case. It proceeds in such a way that the nitrogen atom 2 of the 1,3-dipolar structure **S2** attacks carbon atom 10 of methyl isocyanate. This leads to an ionic intermediate **M1**. Finally, this intermediate is transformed into product **S4** by the bond formation between atoms 4 and 9. The calculated thermodynamic data for the struc-



SCHEME 4

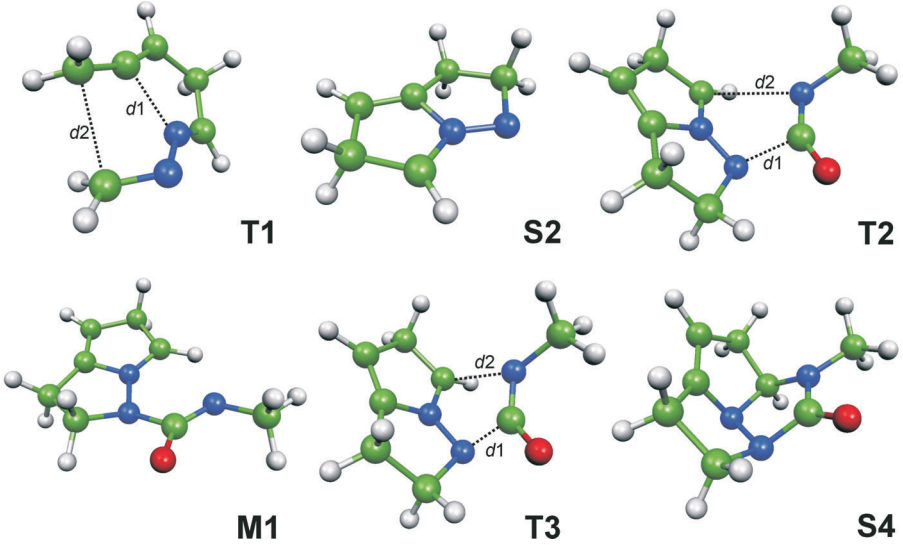


FIG. 1

Representative stationary structures on the potential energy surface of the intra-intermolecular criss-cross cycloaddition. Dashed lines show forming bonds in particular 1,3-dipolar cycloadditions (illustration prepared with MOLEKEL [15])

tures along the reaction pathway are given in Table I. It follows from them that the intramolecular step has almost a twice higher Gibbs activation energy (MP2: 26.7 kcal mol^{-1}) than the subsequent intermolecular step (MP2: 16.3 kcal mol^{-1}). This indicates that the intramolecular step is the rate-determining step of the intra-intermolecular mechanism. From the thermodynamic point of view, both steps are exoergic.

Data in Table I show that the results of B3LYP and MP2 calculations differ. The maximum difference between the activation Gibbs energies (kinetic characterization of the mechanism) is only –2.2 kcal mol^{-1} for the intermolecular step while it is 4.8 kcal mol^{-1} for the intramolecular step. There are also differences between calculated reaction energies (thermodynamic characterization of the reaction). The maximum differences are –4.3 and –9.4 kcal mol^{-1} for the intermolecular and the intramolecular step, respectively. In conclusion, the MP2 method gives lower activation and higher reaction energies than the B3LYP method with the same basis set.

TABLE I

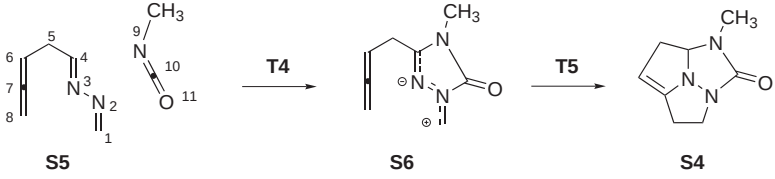
Thermodynamic, kinetic and geometric data and transition-state vibration characteristics calculated for the intra-intermolecular mechanism (electronic energy ΔE, enthalpy ΔH and Gibbs energy ΔG (all in kcal mol^{-1}), distances d_1 and d_2 (in Å) and imaginary frequency ν_{imag} (in cm^{-1}))

Structure	B3LYP/cc-pVDZ						MP2/cc-pVDZ					
	d_1[a]	d_2[a]	ΔE	ΔH	ΔG	ν_{imag}	d_1[a]	d_2[a]	ΔE	ΔH	ΔG	ν_{imag}
S1	3.966	7.106	0.0	0.0	0.0		3.871	6.938	0.0	0.0	0.0	
T1	1.901	2.468	27.4	26.0	31.5	–385.9	1.988	2.525	22.8	21.3	26.7	–316.6
S2	1.456	1.563	–17.2	–15.8	–9.4		1.454	1.557	–27.0	–25.4	–18.8	
S3	3.123	4.591	0	0	0		2.907	3.541	0	0	0	
T2	2.020	2.959	10.2	9.0	14.1	–178.3	1.819	2.799	13.0	11.8	16.3	–158.4
M1	1.515	2.775	5.5	5.5	11.7		1.538	2.761	10.3	10.2	15.3	
T3	1.561	2.399	9.9	9.1	17.1	–156.5	1.606	2.380	14.2	13.4	20.1	–195.9
S4	1.420	1.459	–31.7	–30.1	–20.5		1.431	1.454	–34.8	–33.2	–24.8	

[a] d_1 = d(N3,C7) and d_2 = d(C1,C8) for **S1**→**S2**; d_1 = d(N2,C10) and d_2 = d(C4,N9) for **S3**→**S4**. For atom numbering, see Scheme 4.

Inter-Intramolecular Sequence

Only concerted steps were found in the inter-intramolecular mechanism. The first intermolecular step leading from structure **S5** to the 1,3-dipolar structure **S6** has almost a twice higher activation Gibbs energy than the second intramolecular step connecting the 1,3-dipolar structure **S6** to the final cycloadduct **S4** (Scheme 5, Fig. 2). The data calculated along the reaction pathway are given in Table II.



SCHEME 5

Some discrepancies are seen in Table II. The MP2 electronic energy of the transition state **T5** (intramolecular step) is lower than that of the initial structure **S6**. This however, would show, that something must be wrong in the calculations. Vibrational analysis confirms the correct nature of transition structure **T5** calculated using the MP2 method. Therefore, the structure **S6** calculated on the same level of theory and shown to be a true energy minimum on the MP2 level does not probably represent the initial structure of this step. The problem is most likely caused by the starting structure, which was taken from previous calculations at a different level of theory (B3LYP/6-31G*). The obtained structure **S6** is probably just another conformer of the initial structure. The problem could easily be fixed

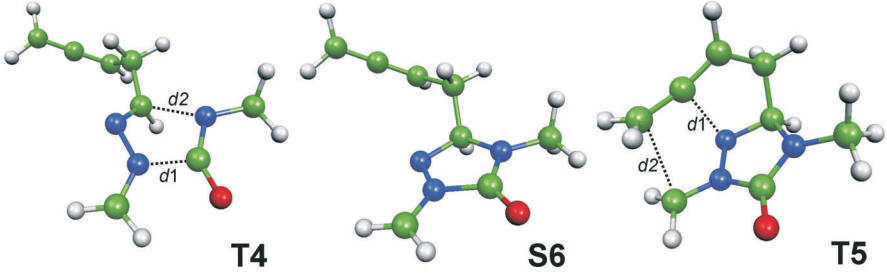


FIG. 2

Representative stationary structures on the potential energy surface of the inter-intramolecular criss-cross cycloaddition. Dashed lines show forming bonds in particular 1,3-dipolar cycloadditions (illustration prepared with MOLEKEL [15])

by using the intrinsic reaction coordinate (IRC) method or by the driving method at MP2 level of theory. We did not perform such calculations because it would be too time-consuming. Instead, we suggest that the B3LYP data is a good upper guess of the correct Gibbs activation energy (13.8 kcal mol^{-1}). This value is still significantly lower than the activation energy of the previous step. Therefore, it can be assumed also here that the intermolecular step is the rate-determining step of the inter-intramolecular mechanism. This mechanism only differs from the previous one only in the reaction energies. While both steps in the previously discussed mechanism were exoergic, in this mechanism the first step is endoergic (MP2: 3.3 kcal mol^{-1}) which is followed by the exoergic one (MP2: –49.1 kcal mol^{-1}).

It follows from the previous data that the first step is always the rate-determining step regardless of the mechanism. The Gibbs activation energy (MP2) for the intra-intermolecular sequence is lower by about 7.5 kcal mol^{-1} compared with that calculated for the inter-intramolecular sequence. This implies that the mechanism is intra-intermolecular. It also follows from calculations at this level of theory that the second (intermolecular) step has a lower Gibbs activation barrier by *ca* 10.4 kcal mol^{-1} compared with the first step. This is in agreement with the experimental observations that the sec-

TABLE II
Thermodynamic, kinetic and geometric data and transition-state vibration characteristics calculated for the inter-intramolecular mechanism (electronic energy ΔE, enthalpy ΔH and Gibbs energy ΔG (all in kcal mol^{-1}), distances d_1 and d_2 (in Å) and imaginary frequency ν_{imag} (in cm^{-1}))

Structure	B3LYP/cc-pVDZ						MP2/cc-pVDZ					
	d_1[a]	d_2[a]	ΔE	ΔH	ΔG	ν_{imag}	d_1[a]	d_2[a]	ΔE	ΔH	ΔG	ν_{imag}
S5	3.744	5.519	0	0	0		2.969	4.480	0	0	0	
T4	1.614	2.148	23.2	22.2	32.9	–215.9	1.646	2.126	25.8	24.9	34.2	–279.3
S6	1.498	1.465	–3.1	–2.3	9.4		1.499	1.454	–7.7	–6.6	3.3	
S6	3.689	6.390	0	0	0		3.443	5.914	0	0	0	
T5	2.166	2.464	9.6	8.6	13.8	–381.1	2.269	2.433	–0.2	–1.1	4.5	–267.3
S4	1.439	1.570	–48.7	–46.6	–39.6		1.446	1.567	–58.9	–56.6	–49.1	

[a] d_1 = d(N2,C10) and d_2 = d(C4,N9) for **S5**→**S6**; d_1 = d(N3,C7) and d_2 = d(C1,C8) for **S6**→**S4**. For atom numbering, see Scheme 5.

ond step of CCC must be faster than the competitive rearrangement of the 1,3-dipolar structure to structure **10**. When the results calculated at the B3LYP level of theory are considered, then the Gibbs activation barriers of both rate-determining steps are almost the same. However, this is still in agreement with the proposed mechanism because the reaction rate also depends on the reaction order. Since the intermolecular step is of the second order and the concentrations of both reacting compounds are low enough, the rate of this intermolecular step will be significantly lower than that of the intramolecular step even if the Gibbs activation energies are the same or very close to each other.

CONCLUSIONS

Two different mechanisms of mixed criss-cross cycloaddition, intra-inter and inter-intramolecular, were explored by quantum-chemical calculations in this study. It was found that the first step is rate-determining regardless of the mechanism. The Gibbs activation barrier of the intramolecular step of the intra-intermolecular sequence is by 10.4 kcal mol^{-1} lower than that of the intermolecular step of the inter-intramolecular sequence at the MP2 level of theory and almost the same at the B3LYP level of theory. This confirms that the mechanism of CCC is intra-intermolecular. The calculated Gibbs activation barrier of the second (intermolecular) step is only 16.3 kcal mol^{-1}, which is in agreement with experimental observations showing that the second step must be fast enough to prevent competitive rearrangement of the 1,3-dipolar structure.

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