



An Overlooked Pathway in 1,3-Dipolar Cycloadditions of Diazoalkanes with Enamines

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Dedicated to Professor Wolfgang Beck on the occasion of his 90th birthday

Abstract: Methyl diazoacetate reacts with 1-(*N*-pyrrolidino)cycloalkenes to give products of 1,3-dipolar cycloadditions and azo couplings. The kinetics and mechanisms of these reactions were investigated by NMR spectroscopy and DFT calculations. Orthogonal π -systems in the 1,3-dipoles of the propargyl-allenyl type allow for two separate reaction pathways for the (3+2)-cycloadditions. The commonly considered concerted pathway is rationalized by the interaction of the enamine HOMO with LUMO+1, the lowest unoccupied orbital of the heteropropargyl anion fragment of methyl diazoacetate. We show that HOMO/LUMO($\pi^*_{N=N}$) interactions between enamines and methyl diazoacetate open a previously unrecognized reaction path for stepwise cycloadditions through zwitterionic intermediates with barriers approximately 40 kJ mol^{-1} lower in energy in CHCl_3 (DFT calculations) than for the concerted path.

Huisgen (3+2)-cycloadditions can be considered to be the most general synthesis for five-membered heterocycles.^[1] They usually proceed via concerted mechanisms, which are rationalized by interactions of the frontier orbitals of the heteroallyl or heteropropargyl anion fragments of the 1,3-dipoles with the frontier orbitals of the dipolarophiles.^[2] Whereas interactions of ψ_2 (1,3-dipole) with LUMO(dipolarophile) are considered to control the reactions of electron-rich 1,3-dipoles with electron-poor dipolarophiles, the interactions of HOMO(dipolarophile) with ψ_3 (1,3-dipole) have been assumed to be dominating in

reactions of electron-rich dipolarophiles with electron-deficient 1,3-dipoles (Figure 1).

In diazoalkanes, however, ψ_3 does not correspond to LUMO, but to LUMO+1, since the perpendicular $\pi^*_{N=N}$ is lower in energy (Figure 1). Hamlin and co-workers have already reported this ordering of orbitals in diazomethane and stated that in the reaction of diazomethane with ethylene “the orientation of the LUMO of diazomethane, being perpendicular to the HOMO(ethylene), prevents it from overlapping in a favorable manner and thus the HOMO(ethylene)-LUMO+1(diazomethane) interaction dominates”.^[2b] Chen, Hu, and Houk also reported that the lowest unoccupied orbital of the heteropropargyl fragment (ψ_3) does not correspond to the LUMO of diazomethane. They did not comment, however, why the interaction with the LUMO of diazomethane was neglected in their analysis.^[2i] We now report that the 1,3-dipolar cycloadditions of methyl diazoacetate (**1**) with electron-rich dipolarophiles may proceed via different pathways arising from interactions of the enamines’ HOMO with either LUMO or LUMO+1 of the diazoalkane.

Reissig obtained 15% of pyrazole **3a** when methyl diazoacetate (**1**) and pyrrolidinocyclopentene (**2a**) were heated under reflux in chloroform and subsequently treated with HCl in methanol (Scheme 1).^[3a] The formation of a mixture of (*E/Z*)-isomers of **4a** was reported, when the same experiment was carried out at 0 °C and worked up by chromatography.^[3a] Since cyclization was not observed when the hydrazoneenamine obtained from **1** and 1-(*N*-morpholino)cyclopentene (that is, the non-hydrolyzed precursor of **4a**) was treated with acid, the direct formation of **3a** through concerted cycloaddition was postulated.^[3a] X-ray

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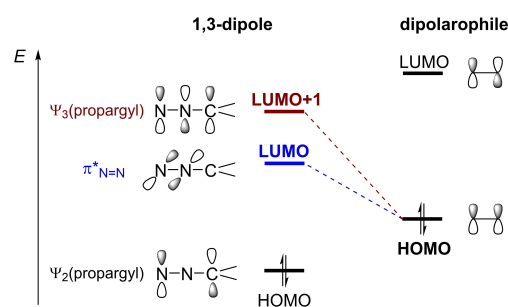
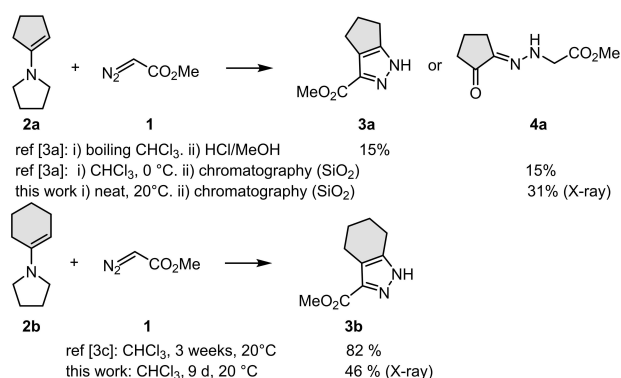


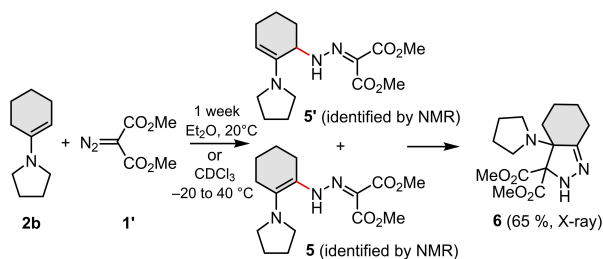
Figure 1. Qualitative description of orbital interactions of electron-rich dipolarophiles with acceptor-substituted diazoalkanes.



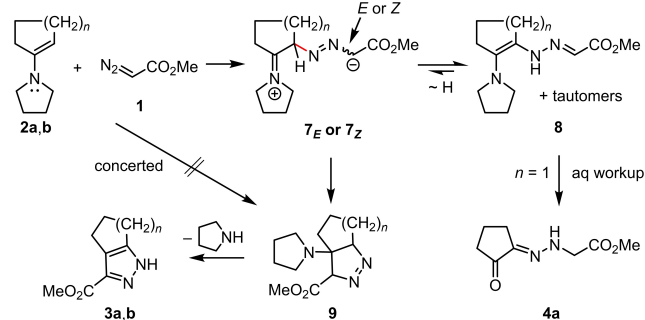
Scheme 1. Products of the reactions of methyl diazoacetate (**1**) with enamines **2a** and **2b**.

analysis and NMR spectra of **4a**, which we obtained by combining **1** and **2a** without solvent at room temperature, showed the presence of a single isomer of **4a** (Supporting Information).

The formation of 82 % of pyrazole **3b** by the reaction of **1** with **2b** at room temperature was reported by Huisgen and Reissig.^[3c] While our experiments confirmed the formation of **3b**, NMR monitoring of this reaction showed signals of unidentified intermediates before the appearance of the signals of **3b** (Supporting Information, Figure S2). In order to elucidate the nature of the unidentified intermediates we investigated the analogous reaction of diazomalonate **1'** with **2b** by NMR spectroscopy (Scheme 2).



Scheme 2. NMR monitoring of the reaction of **1'** with enamine **2b** (¹H NMR spectra are shown in Supporting Information, Figure S3).



Scheme 3. Proposed mechanism for the reactions of **1** with enamines **2a,b**.

When Huisgen and Reissig kept a solution of **2b** and **1'** in diethyl ether for four days at room temperature, they obtained the bicyclic pyrazoline **6** in 73 % yield.^[3a,c] Accordingly, in this work, **6** was isolated in 65 % yield (Et₂O, one week at room temperature) and characterized by X-ray analysis (Scheme 2). Monitoring this reaction by ¹H NMR spectroscopy in CDCl₃ showed that initially the reactants were quantitatively converted into a mixture of hydrazonoenamines **5** and **5'**, which subsequently underwent cyclization with formation of **6** (Supporting Information, Figure S3). We, therefore, suggest that all reactions in Schemes 1 and 2 proceed by the mechanism illustrated in Scheme 3 and disagree with earlier conclusions that pyrazolines **6** and **9** are formed via concerted 1,3-dipolar cycloadditions.^[3]

Electrophilic attack of the diazo ester **1** at the enamines **2** yields zwitterions **7**, which may undergo proton shifts to yield **8** or several other tautomers whose hydrolyses give hydrazonocyclopentanone **4a**. Pyrazoline **9**, the supposed precursor of **3**, is formed in a subsequent process by cyclization of zwitterions **7**, which may be regenerated through proton shifts from **8** or its tautomers. The reason why this cyclization is more favorable in the reaction with **2b** than with **2a** is discussed in the computational section below.

The kinetics of the reactions of methyl diazoacetate (**1**) with the enamines **2a** and **2b** were investigated by time-resolved ¹H NMR spectroscopy, following the decrease of the vinylic hydrogens of the enamines **2** relative to an internal standard (1,1,2,2-tetrachloroethane) in CDCl₃ at low temperatures. Equimolar amounts of **1** and **2** were used, and the second-order rate constants k_2 were obtained as the slopes of plots of $1/[2]_t$ versus time t according to $1/[2]_t = k_2 t + 1/[2]_0$ (Figure 2a).^[4]

Plots of $\ln(k_2/T)$ versus $1/T$ provided the Eyring activation parameters ΔH^\ddagger and ΔS^\ddagger in CDCl₃ (Figure 2b), from which the second-order rate constants k_2 at +80.3 °C were extrapolated that gave values 3 and 12 times higher than reported^[3a,d] for this temperature in toluene (Table 1). Table 1 shows that both reactions **1** + **2a,b** are characterized by highly negative activation entropies, again demonstrating that highly negative activation entropies cannot be used as a criterion for the occurrence of multicenter processes.^[5]

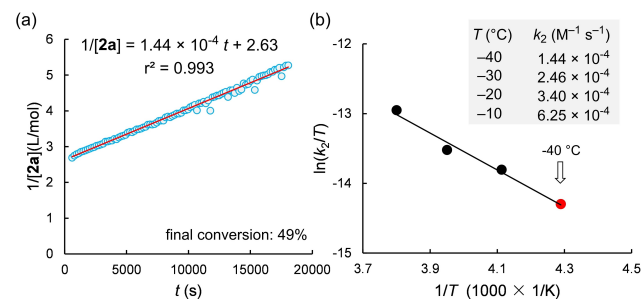


Figure 2. a) Kinetics of the reaction of **1** (0.399 M) with **2a** (0.371 M) monitored by the decrease of the NMR signals of the vinylic H of **2a** vs. 1,1,2,2-tetrachloroethane (0.276 M) as internal standard in CDCl₃ at -40 °C. b) Eyring plot for the reactions of **1** with **2a** at -40 to -10 °C.

Table 1: Second-order rate constants k_2 in CDCl_3 for the reactions of **1** with **2a, b** at various temperatures, and k_2 at +25 and +80.3 °C calculated from the Eyring activation parameters ΔH^\ddagger and ΔS^\ddagger .

Enamine	T [°C]	k_2 [$\text{M}^{-1} \text{s}^{-1}$]	ΔH^\ddagger [kJ mol^{-1}]	ΔS^\ddagger [$\text{J mol}^{-1} \text{K}^{-1}$]
2a	-40	1.44×10^{-4}	22.0 ± 2.1	-222 ± 9
	-30	2.46×10^{-4}		
	-20	3.40×10^{-4}		
	-10	6.25×10^{-4}		
	+25	2.17×10^{-3} [a]		
	+80.3	1.03×10^{-2} [a]		
2b	+80.3	8.28×10^{-4} [b]	23.5 ± 1.8	-228 ± 7
	-30	5.46×10^{-5}		
	-20	8.48×10^{-5}		
	-10	1.43×10^{-4}		
	+25	5.59×10^{-4} [a]		
	+80.3	2.91×10^{-3} [a]		
	+80.3	8.90×10^{-4} [b]		

[a] Extrapolated from rate constants at lower temperatures in this table by using the Eyring equation. [b] k_2 in toluene, as reported in refs. [3a,d].

After an extensive conformational search^[6] the geometries of all structures were optimized at the B3LYP-D3BJ/def2-SVP^[7] level of theory considering solvation with the SMD model^[8] for chloroform within the Gaussian set of codes.^[9] For improved accuracy, the thermal corrections at this level were combined with single-point energies using the (SMD = CHCl_3)/MN15/def2-TZVPD method.^[10] Lastly, the Gibbs energies of all conformers were Boltzmann weighted.

Let us first consider the reaction of methyl diazoacetate (**1**) with pyrrolidinocyclopentene (**2a**). Diazoacetate **1** exists as two almost isoenergetic conformers which interconvert via a rotational barrier of 52.2 kJ mol^{-1} (at 25 °C) as determined by NMR spectroscopy and confirmed by DFT calculations (Figure 3a).^[11]

Figure 3b replaces the qualitative orbital representations of LUMO and LUMO + 1 for 1,3-dipoles in Figure 1 by the calculated images of these two orbitals for **1**.^[12] As expected, $\pi^*_{\text{N=N}}$ (LUMO) is significantly lower in energy than LUMO

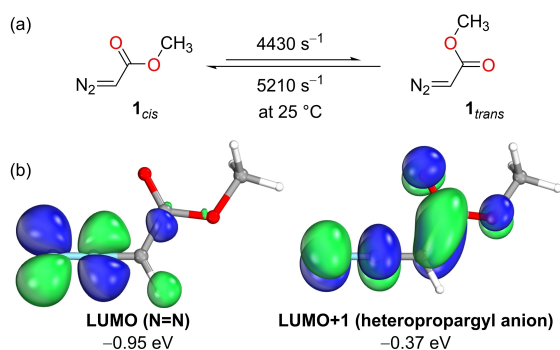


Figure 3. a) Conformational equilibrium of methyl diazoacetate (**1**) experimentally determined by dynamic ^1H NMR spectroscopy in CDCl_3 .^[11] b) Lowest unoccupied molecular orbitals of **1** and their energies at the (SMD = CHCl_3)/MN15/def2-TZVPD// (SMD = CHCl_3)/B3LYP-D3BJ/def2-SVP level of theory.

+1, independent of the computational method and basis set (see Supporting Information for a systematic investigation).

Interaction of the enamine HOMO with LUMO+1 of **1_{trans}** directly leads to the (3+2)-cycloadduct as illustrated in Figure 4a. For the location of the transition state of this trajectory, the C–N and C–C bonds of the cycloadduct were simultaneously elongated. The structure lying at the saddle point of the resulting three-dimensional energy surface was further optimized to give a transition state, where the formation of the new C–N bond (1.85 Å) is much further advanced than that of the new C–C bond (2.77 Å).

The intrinsic reaction coordinate (IRC) shows that after passing the transition state, the C–N bond continues to shorten much faster than the C–C bond. Though the resulting structures closely resemble a zwitterion, a local minimum for an intermediate is not involved, and the C–C bond is formed without additional barrier.

A slightly more favorable concerted pathway arises from interaction of HOMO(**2a**) with LUMO+1 of **1_{cis}**. The corresponding transition state shows a higher degree of asynchronicity (Figures S8 and S9; C–N bond: 1.73 Å, C–C bond: 3.14 Å) and the reaction might be considered as a two-step no-intermediate process. Detailed discussions of the concerted mechanisms are shifted into the Supporting Information, because none of them is followed in reality.

The actually occurring reaction pathway (Figure 4b^[15]) arises from the interaction of the HOMO(enamine) with $\pi^*_{\text{N=N}}$, that is, the LUMO of **1**, as substantiated by analysis of the overlap integrals of the involved orbitals.^[13,14] This pathway leads to the formation of zwitterion **7_Z** faster than to its isomer **7_E** despite the higher thermodynamic stability of the latter (for geometries and charges of zwitterions **7**, see Figure S11). Transition state **TS_Z**, which is 51 and 42 kJ mol^{-1} lower in Gibbs energy than the transition states **TS_{conc}** of the two concerted cycloadditions, was located by stepwise elongation of the C–N bond in the zwitterion **7_Z** and optimization of the structure at the energetic maximum of the resulting pathway on the potential energy surface. As cyclization of **7_Z** occurs with a smaller barrier ($\Delta E_{\text{rel}} = 7.7$, $\Delta G^\ddagger = 26 \text{ kJ mol}^{-1}$) than the retroaddition regenerating the reactants, the formation of **7_Z** via **TS_Z** corresponds to the rate-determining step of the stepwise cycloaddition (Figure 5a).^[16] Thus, the stepwise cycloaddition in Figure 4b is highly preferred over the concerted pathway in Figure 4a.

However, the isolation of hydrazonocyclopentanone **4a**, a hydrolysis product of **8** in the reaction of **1** with **2a**, implies that proton shifts in the zwitterion **7_Z** or **7_E** must be even faster than cyclization. Since calculations revealed a high barrier for the intramolecular 1,2-proton shift from **7** to **8**,^[17] intermolecular processes must account for these tautomerizations, as previously reported for the 1,2-proton shifts generating Breslow intermediates from the zwitterions initially formed from aldehydes and NHCs.^[18] Because of the manifold of potential intermolecular proton shifts, we have not tried to calculate barriers for these proton shifts, at least one of which must be even smaller than the low barriers calculated for the cyclizations of **7_Z**.

Comparison of the two Gibbs energy profiles in Figure 5 shows close similarity for the reactions of **1** with the

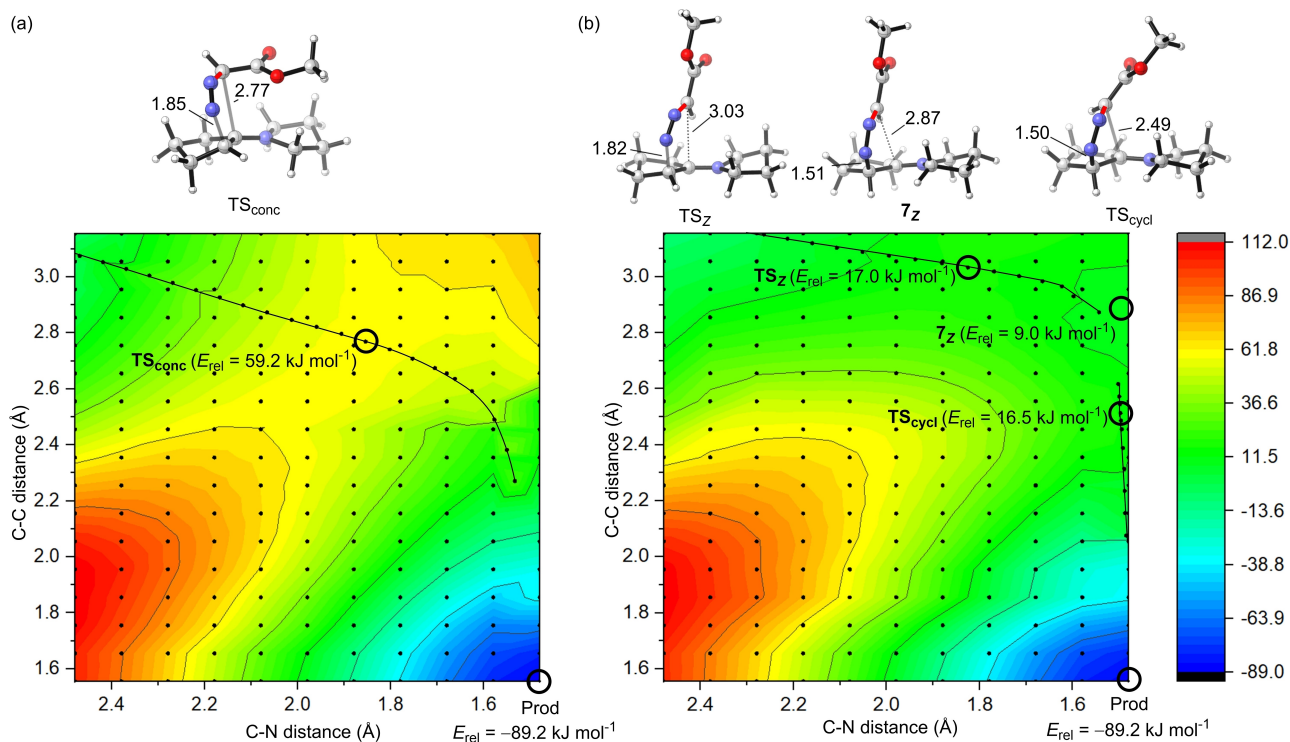


Figure 4. 3D potential energy surfaces at the (SMD=CHCl₃)/B3LYP-D3BJ/def2-SVP level for the reaction of methyl diazoacetate (**1**_{trans}) with pyrrolidinocyclopentene (**2a**) for (a) the concerted pathway (for the related surface with **1**_{cis}, see Figure S9b) and (b) the stepwise pathway. All energies E_{pot} (in kJ mol⁻¹) are given relative to the reactants and are scaled identically for both pathways. Isolines are drawn at an energy difference of 25 kJ mol⁻¹. Black lines connect the reaction pathway derived from IRC calculations starting from the respective transition states. Note: Since zwitterion **7**_z is located on a flat region of the potential energy surface, relaxation of **TS**_z by means of an IRC calculation did not end up exactly at **7**_z, but stopped in close vicinity to **7**_z due to the low gradient in the surroundings.

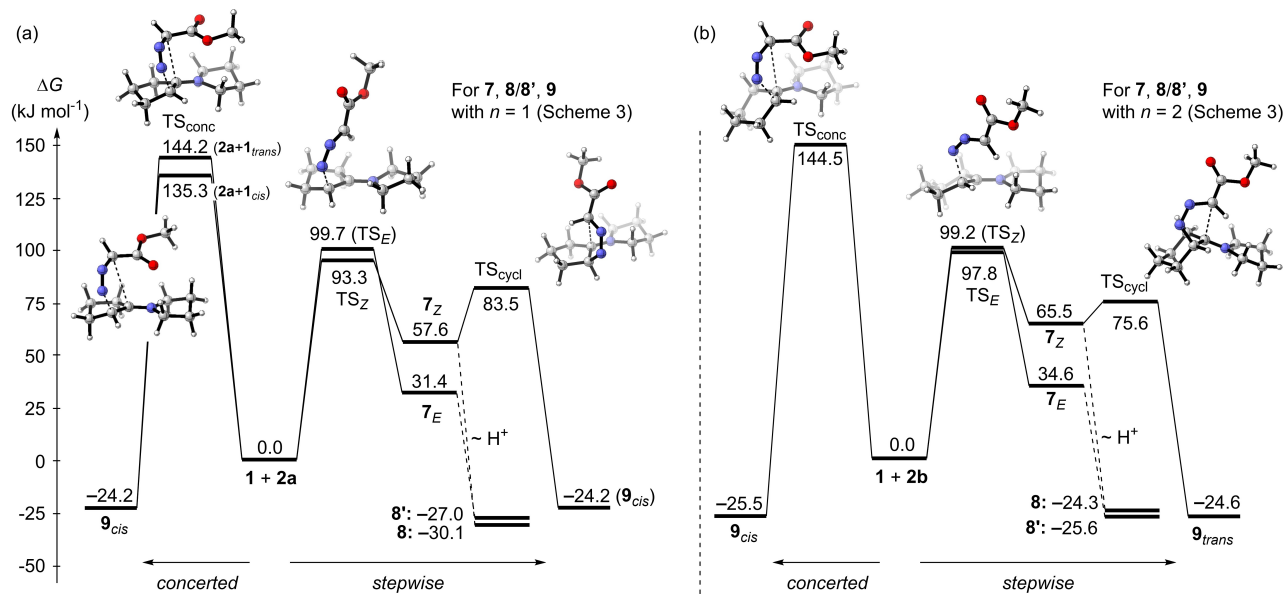


Figure 5. Comparison of the Gibbs activation energies ΔG (kJ mol⁻¹) of the concerted and stepwise cycloadditions of **1** with **2a** (a) and **2b** (b) as computed at the (SMD=CHCl₃)/MN15/def2-TZVPD//((SMD=CHCl₃)/B3LYP-D3BJ)/def2-SVP level of theory. In **9**, *cis* and *trans* refer to the relative orientation of the pyrrolidine and ester moieties. Less favorable **TS**_{cycl} are shown in Figures S7 and S10.

enamines **2a** and **2b**. In both cycloadditions, the stepwise process with rate-determining formation of the zwitterion **7**

is highly favored over the concerted processes. The agreement of the experimentally determined activation Gibbs

energies $\Delta G^{\ddagger}_{\text{exp}}$ (298 K) of 88 (**1+2a**) and 92 kJ mol⁻¹ (**1+2b**) with the calculated barriers for the formation of the zwitterions **7** (93 and 98 kJ mol⁻¹, respectively) leads to the conclusion that *zwitterions 7 are common intermediates for cycloadditions (→9) and azo couplings (→8)*.

A distortion/interaction analysis^[19] for the reaction **1+2a** shows that the higher activation barrier for the concerted pathway is predominantly caused by the higher distortion energy of methyl diazoacetate **1** (Figures S12 and S13). The differences of the interaction energies are much smaller but are also in favor of the stepwise pathway. Further energy decomposition analysis of the interaction energies with the SAPT method^[20] shows that in addition to its higher steric constraints, it is predominantly Pauli repulsion that disfavors the concerted pathways (Figures S14 and S15).^[21]

Figure 5 rationalizes why the azo-coupling products initially formed from aminocyclohexene **2b** cyclize under the reaction conditions, while those obtained from aminocyclopentene **2a** do not. Since the proton shifts in the zwitterions **7** (→**8** or **8'**) were experimentally found to be faster than their cyclizations, one can conclude that the equilibration of **8** and **8'** with **7_E** and **7_Z** is faster than the cyclizations. Thus the Curtin–Hammett principle applies, and one can calculate barriers of 113.6 (Figure 5a) and 101.2 kJ mol⁻¹ (Figure 5b) for the formation of **9** from the more stable of the azo coupling products **8** or **8'** (difference between **8** or **8'** and TS_{cycl}). The differences of the Gibbs energies in Figures 5a and b are thus in line with the observation of different types of products in reactions of diazoalkanes with five- and six-membered enamines, but cannot be considered as definite proof because of the error limits of the computed energies. Since the pyrazolines **9** undergo further stabilization by elimination of the amines and proton shifts, the relative Gibbs energies of **8/8'** and **9** do not account for the different behavior of 5- and 6-membered enamines. Formation of **9** via electrocyclicization of an N-alkenyl azomethine imine, a tautomer of **8**, was calculated to have a much higher barrier than the pathway via cyclization of **7** (Supporting Information, p S37).

What is the link between the two trajectories depicted in Figures 4a and b? Rotation around the red C–N bond in TS_Z of the stepwise process (while the C–N bond length is constrained to 1.83 Å and the C–C bond length to 3.03 Å) transforms TS_Z (Figure 4b) into a structure similar to the structure of TS_{conc}, the transition state of the concerted cycloaddition in Figure 4a. In the initial phase of this rotation, which corresponds to a change of the N=N–C–C dihedral angle from 180° (in TS_Z) to roughly 260° or 100°, the potential energy increases by 55–58 kJ mol⁻¹ due to loss of the partial double-bond character of the red bond. Further rotation leads to a decrease of energy by approximately 11 kJ mol⁻¹ due to interaction of the termini of the incipient zwitterion. This barrier accounts for the existence of separate concerted and stepwise trajectories, as quantitatively described in Figure S16.^[22]

The question whether 1,3-dipolar cycloadditions proceed by concerted (Huisgen)^[23b,24a] or stepwise mechanisms (Firestone)^[23a] has been a long-lasting controversy. While Huisgen rejected Firestone's diradical hypothesis in

general,^[23b] in 1986 Huisgen, Mloston, and Langhals reported the first nonstereospecific 1,3-dipolar cycloadditions in reactions of thiocarbonyl ylides with electron-acceptor substituted ethylenes, which they interpreted by stepwise processes via intermediate zwitterions.^[25] Nevertheless, the concerted mechanism of most 1,3-dipolar cycloadditions is now well established, and their rates are commonly rationalized by the interactions of the frontier orbitals of the allyl/propargyl fragment of the 1,3-dipoles with the frontier orbitals of the dipolarophiles.^[2]

Reaction rates of acceptor-substituted diazoalkanes, such as **1** and **1'**, have been the preferred examples to illustrate this FMO model,^[24] probably because these 1,3-dipoles display the most spectacular variations of reactivity – fast reactions with electron-deficient dipolarophiles (acrylic esters) as well as with electron-rich dipolarophiles (enamines), and slow reactions with alkyl- and alkoxy-substituted ethylenes (Figure 3 in ref. [3d]). Our work has shown, however, that *these examples are not suitable for demonstrating the dependence of cycloaddition rates on the interactions of the frontier orbitals of the dipolarophiles with the frontier orbitals of the 3-center/4-electron π -systems in 1,3-dipoles, because (1) the measured rate constants with enamines refer to azo-couplings, not to cycloadditions, and (2) the reactions with enamines are not controlled by HOMO(dipolarophile)- Ψ_3 (1,3-dipole) interactions, but by interactions of HOMO(enamine) with $\pi^*_{\text{N=N}}$, the LUMO of methyl diazoacetate, an orbital whose role has so far been neglected.*

We now found that the availability of two perpendicular low-lying unoccupied molecular orbitals in acceptor-substituted diazoalkanes (e.g. **1** and **1'**) opens the possibility for nucleophilic attack at two different orbitals. Interaction of the enamines' HOMO with LUMO+1(diazoacetate) is calculated to result in concerted (3+2)-cycloadditions through transition states which are considerably higher in energy than the experimentally observed stepwise processes with formation of the zwitterions **7**, which proceed by attack of the enamines at LUMO($\pi^*_{\text{N=N}}$) of the diazoalkanes. This situation thus differs from most other concomitant concerted and stepwise cycloadditions, where both pathways are controlled by the interactions of the same orbitals and only differ by unlike orientations of the reactants (cyclic vs stretched).

We are presently investigating the switch from stepwise cycloadditions (attack at LUMO of diazoalkane) to concerted cycloadditions (attack at LUMO+1 of diazoalkane), which is expected to take place when enamines are replaced by less nucleophilic dipolarophiles. Furthermore, we are exploring the role of the two perpendicular π -orbitals in (3+2)-cycloadditions of other 1,3-dipoles of the propargyl/allenyl type (e.g., azides).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Diazoalkane · Enamine · Kinetics · Orbital Interactions · Quantum Chemical Calculations

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