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1,3-Dipolar Cycloaddition Reactions of Stable Bicyclic and Monocyclic Azomethine Ylides: Kinetic Aspects

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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Abstract—Kinetic data for 1,3-dipolar cycloadditions of stable azomethine ylides **1**–**3** with angle-strained, electron-poor and electron-rich 2π-components **4**–**10** prove that most reactions are $LUMO_{dipole}$–$HOMO_{dipolarophile}$-controlled. Small ρ-values and a minor solvent effect on the rate constants are in accord with a concerted bond formation in the transition state.

Introduction

Azomethine ylides, in many cases only existing as reactive intermediates and trapped after in situ preparation mostly by electron-poor dipolarophiles, are of great synthetic value.[1–5] These cycloadditions proceed with high stereochemical selectivity leading to pyrroline and pyrrolidine derivatives that are central skeletons of numerous alkaloids. In spite of the high preparative importance of these reactions detailed kinetic studies are rare. Huisgen reports kinetic data for a Münchnone derivative,[6] for a crystalline azomethine ylide derived from 3,4-dihydroisochinoline the rate constants and the activation parameters are available for the addition to dimethyl acetylenedicarboxylate at different temperatures.[7]

Quite recently we reported a productive entrance to new stable bicyclic (**1**) and monocyclic (**2**) azomethine ylides.[8–11] These highly coloured 1,3-dipoles readily add to angle-strained, electron-rich and electron-poor dipolarophiles.[12] With enamines as 2π-components nonstereospecific 1,3-dipolar cycloadditions were observed which could be best explained by a two-step mechanism via zwitterionic intermediates.[13]

In this communication we give full report on kinetic investigations with stable 1,3-dipoles **1**–**3** studying the substituent effects in the azomethine ylides and the dipolarophiles used as well as the solvent influence on the rate constants.

Results

In the course of the [3+2] cycloadditions of azomethine ylides **1**–**3** with dipolarophiles **4**–**10** the colour of the dipole disappears (Scheme 1). So it is quite easy to monitor the reactions by the disappearance of the intense π–π* absorption of the azomethine ylides in the visible range. All cycloadditions studied kinetically in this contribution clearly follow a second-order rate law between 10% and mostly more than 90% conversion. Tables 1–3 offer the rate data for the variation of the substituents *R* in azomethine ylides **1**–**3** for three selected dipolarophiles, the angle-strained cyclooctyne (**4**), the electron-rich ynamine **5**, and the electrophilic dimethyl acetylenedicarboxylate (**6**). Some interesting phenomena are evident and should be stated briefly.

(1) The bicyclic azomethine ylides **1** prefer to react with electron-rich dipolarophiles **4** (ρ=1.44, r=0.990) and **5** (ρ=1.69, r=0.994), for the electron-poor dipolarophile **6** (ρ=0.464, r=0.975) the rate constants drop considerably (Table 1). Also heterocycles as substituents (**1f**–**1h**) influence the rate in the direction expected. The logarithms of the rate constants correlate linearly with the half-wave reduction potentials $E_{1/2}$[11] of the azomethine ylides **1a**–**1e** used. The rate data of Table 1 are all in accord with the assumption of a $LUMO_{dipole}$–$HOMO_{dipolarophile}$-control for these 1,3-dipolar cycloadditions.

(2) The rate constants for azomethine ylides **2** of Table 2 show the uniform picture of Table 1 in principle. Regarding the different solvent used (**4**: dioxane; **5**: acetonitrile) cyclooctyne (**4**) and ynamine **5** are of similar reactivity. The ρ-values obtained using σ-values for the substituents *R* show only low correlation coefficients (**4**: ρ=1.35, r=0.977. **5**: ρ=0.898, r=0.962) which are slightly

Keywords: azomethine ylides; 1,3-dipolar cycloadditions; kinetics; solvent effects; linear free energy relations.

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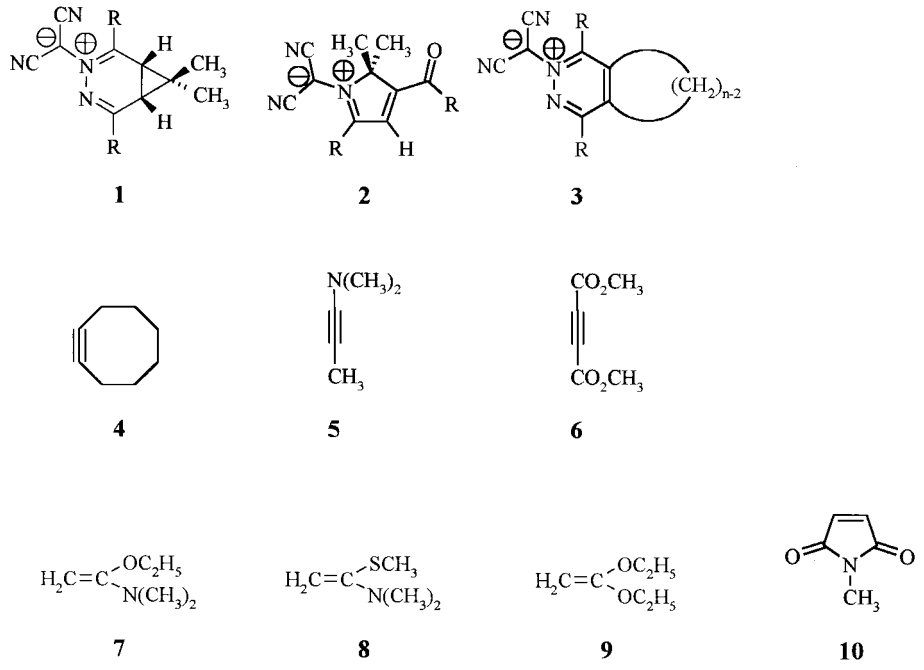
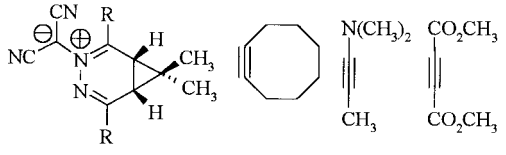
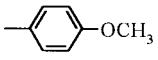
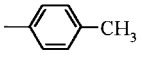
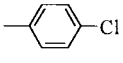
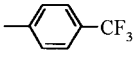


Scheme 1. Azomethine ylides **1**–**3** and dipolarophiles **4**–**10** used in this kinetic study (for *R* and *n* see Tables 1–4).

Table 1. Cycloadditions of azomethine ylides **1a**–**1i** with dipolarophiles **4**–**6** at 20°C in dioxane; values for $10^4 \times k_2$ (l mol^{-1} s^{-1}]

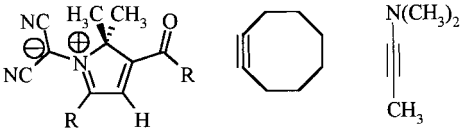


1: R =	**4**	**5**	**6**
a 	122	574	2.94
b 	240	1210	3.96
c 	436	2140	4.02
d 	799	5180	5.11
e 	2080	15300	7.72
f 	6.73	22.3	-
g 	706	1210	-
h 	206	9190	-
i $-SCH_3$	2180	1550	2.20

improved plotting log k_s/k_0 against Brown's σ^+-values (**4**: ρ=0.872, r=0.996. **5**: ρ=0.583, r=0.988). In both cases the cycloadditions follow a $LUMO_{dipole}$–$HOMO_{dipolarophile}$-control.

(3) Table 3 offers rate constants for cycloadditions of the aromatic azomethine ylides **3**. It is evident that the reactivity of the dipoles is sharply reduced. Interestingly, the substituent effect for **3a**–**3d** is reversed passing from cyclooctyne (**4**) (ρ=0.73, r=0.999, correlation with σ-values)

Table 2. Cycloadditions of azomethine ylides **2a**–**2f** with dipolarophile **4** in dioxane and **5** in acetonitrile at 20°C; values for $10^4 \times k_2$ (l mol^{-1} s^{-1})



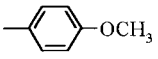
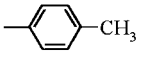
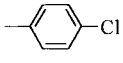
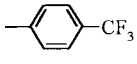
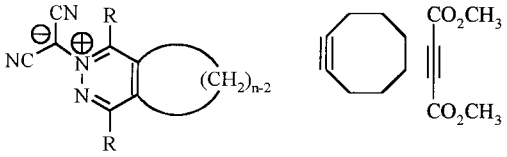
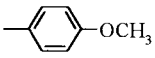
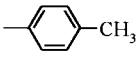
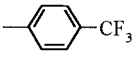
2: R =	**4**	**5**
a 	14.1	900
b 	30.1	1600
c 	58.5	2470
d 	88.7	3620
e 	216	5430
f 	25.2	60.8

Table 3. Cycloadditions of azomethine ylides **3a**–**3e** with dipolarophiles **4** and **6** in dioxane at 20°C; values for $10^4 \times k_2$ (l mol^{-1} s^{-1})



	3: R =	n	4	6
a		5	2.39	2.43
b		5	2.85	1.65
c		5	3.59	1.20
d		5	9.02	0.570
e		6	7.48	5.41

to the electron-poor diester **6** (ρ=−0.45, r=0.991, correlation with σ^+-values). The $LUMO_{dipole}$–$HOMO_{dipolarophile}$-control observed for cyclooctyne (**4**) switches to the inverse $HOMO_{dipole}$–$LUMO_{dipolarophile}$-control for **6**.

(4) Table 4 compares rate data for the 1,3-dipolar cycloaddition of azomethine ylide **1b** with various dipolarophiles **4–10**. As to be expected for a $LUMO_{dipole}$–$HOMO_{dipolarophile}$-controlled reaction donor-substituted 2π-components turn out to be more reactive than acceptor-substituted ones. In principle, the rate constants follow the same order which is also found in the field of [4+2] cycloadditions with inverse

Table 4. Cycloadditions of azomethine ylide **1b** with dipolarophiles **4**–**10** in dioxane at 20°C; values for $10^4 \times k_2$ (l mol^{-1} s^{-1})

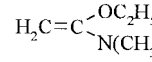
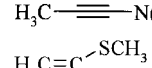
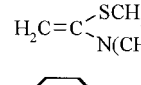
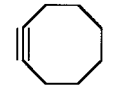
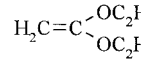
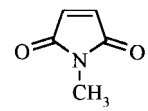
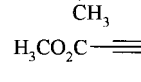
	Dipolarophile	10^4*k_2 [l*mole^{-1}*s^{-1}]
7		25780
5		1211
8		921
4		240
9		4.70
10		4.03
6		3.96

Table 5. Cycloadditions of azomethine ylide **1c** with dipolarophiles **4**–**6** in different solvents; values for $10^4 \times k_2$ (l mol^{-1} s^{-1}) at 20°C

Solvent	E_T	4	5	6
Toluene	33.9	702	838	9.14
Dioxane	36.0	435	2000	4.65
Chlorobenzene	36.8	402	4930	4.82
Tetrahydrofuran	37.4	233	2200	3.04
Ethyl acetate	38.1	311	2550	3.96
1,2-Dimethoxyethane	38.2	225	2980	2.06
Chloroform	39.1	152	7010	1.63
Dichloromethane	40.7	150	12800	1.57
Nitrobenzene	41.2	104	29400	1.60
Benzonitrile	41.5	158	33300	2.07
Acetone	42.2	148	15600	2.15
N,*N*-Dimethylformamide	43.8	86.9	29500	4.58
Dimethylsulfoxide	45.1	97.9	74000	3.20
Acetonitrile	45.6	122	57900	2.23

electron demand using 1,2,4,5-tetrazines as 4π-partners:[14] Ketene N,O- and N,S-aminal **7** and **8** surpass ketene O,O-acetal **9**, ynamine **5** proves to be highly reactive; *N*-methylmaleimide (**10**) and dimethyl acetylenedicarboxylate (**6**) hold the last position in the reactivity sequence.

(5) Finally, we studied the influence of a solvent variation on the cycloaddition rate. Table 5 presents the rate constants for the bicyclic azomethine ylide **1c** in combination with cyclooctyne (**4**), the ynamine **5** and dimethyl acetylenedicarboxylate (**6**) for 15 different solvents which are arranged according to increasing E_T-values.[15] Fig. 1 offers a graphical presentation for a quick survey.

The greatest sensitivity of the rate constants for a solvent variation is found for ynamine **5** with a factor of 88 for $k_{DMSO}/k_{toluene}$; polar solvents increase the cycloaddition rate. In contrast, the addition of cyclooctyne (**4**) to **1c** shows a mild negative solvent effect favouring toluene by a factor of 8.08 ($k_{toluene}/k_{DMSO}$) in comparison with DMSO. Finally, for dimethyl acetylenedicarboxylate (**6**) the rate constants for different solvents show only a scattering, the solvent dependence of the cycloaddition rate coming close to zero.

Discussion

CNDO/2 calculations for the parent azomethine ylide $H_2C{=}N^+H{-}CH_2^-$ resulted in values for HOMO=−6.9 and LUMO=+1.4 (all orbital energies in (eV)).[3] AM1 calculations gave quite similar values: HOMO=−7.3, LUMO=+2.4.[16] Tsuge and Kanemasa concluded that 'due to the narrow frontier orbital separation the parent ylide will be able to react with both electron-deficient and electron-rich dipolarophiles'.[3] In most cases $HOMO_{dipole}$–$LUMO_{dipolarophile}$-controlled reactions are observed: 'Dipolarophiles most frequently employed in trapping of azomethine ylides are acetylenedicarboxylates and maleimides because they are much more reactive than most other dipolarophiles. Maleic anhydride is almost equal to maleimide in reactivity toward azomethine ylides, and fumarates and maleates rank next'.[3] Huisgen's kinetic data obtained for Münchnones are in line with this statements.[6,7]

Electron withdrawing groups in general lower the HOMO-

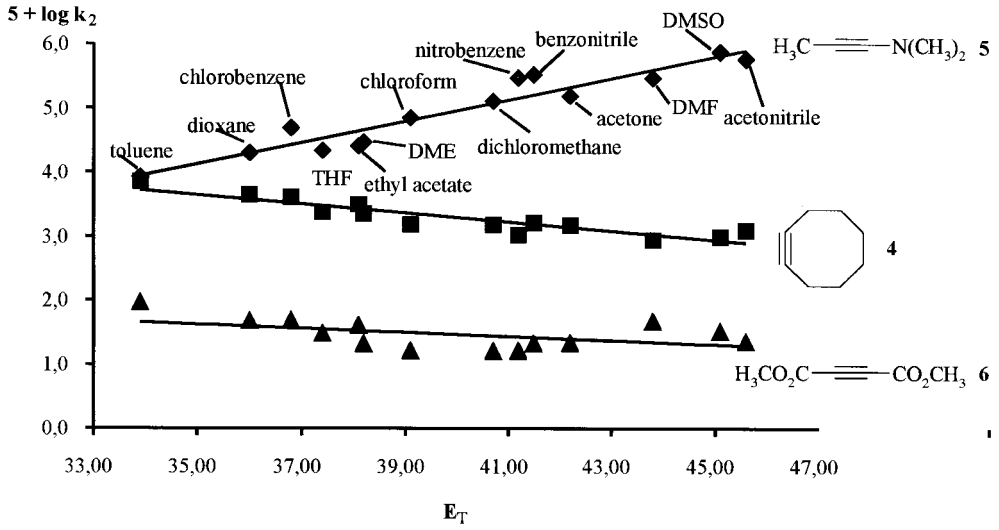


Figure 1. Solvent dependence of the reaction rate: reaction of the bicyclic azomethine ylide **1c** with dipolarophiles **4**, **5** and **6**.

and LUMO-energies. For azomethine ylide **1b** we calculated according to the AM1 procedure HOMO=−7.77 and LUMO=−1.54 (eV). Because of the drastic decrease for the LUMO-energy one would expect to find transition from normal 1,3-dipolar cycloadditions to those with inverse electron demand. This is clearly observed. A comparison of the absolute rate data in Tables 1 and 2 shows high reactivity for the electron-rich dipolarophiles **4** and **5**; furthermore, the influence of substituents *R* in **1** and **2** clearly proves a $LUMO_{dipole}$–$HOMO_{dipolarophile}$-control for these cycloadditions. This is also in line with the observation that log *k*-values correlate in a linear manner with the half wave reduction potentials $E_{1/2}$[11] as a relative measure for the LUMO energies of the azomethine ylides. Also the high reactivity of ketene aminals (see Table 4) are to be expected for the $LUMO_{dipole}$–$HOMO_{dipolarophile}$-control.

Interestingly, the rate constants for the cycloaddition of cyclooctyne (**4**) with the *aromatic* azomethine ylides **3** drop to the values typical for acetylenedicarboxylate **6**. Furthermore, the substituent influence of *R* in **3** is opposite for both reactions. The negative ρ-value for the cycloaddition **3**+**6** is indicative that now this systems obeys the 'normal rules' for azomethine ylide cycloadditions, a $HOMO_{dipole}$–$LUMO_{dipolarophile}$-control.

Solvent effects on rate give insight into the polarity change passing from the ground state to the transition state. Azomethine ylides show rather high dipole moments, i.e. **1b**=13.2 (D), **1c**=12.5 (D), **2b**=11.3 (D), **2c**=10.8 (D),[11] while for the cycloadducts rather diminished values are found,[17] i.e. adduct **1c**+**4**=8.0 (D), **1c**+**5**=8.6 (D). The solvent effect on the cycloaddition rate, as documented in Table 5 demonstrates for cyclooctyne (**4**) and the acetylenedicarboxylic ester **6** that the polarity has not changed too much in the transition state which seems to be early on the reaction coordinate, for ynamine **5** as dipolarophile a slight but distinct increase can be stated. In all three systems the kinetic data are in accord with a concerted bond formation.

Conclusion

Almost all azomethine ylides studied in this contribution undergo concerted $LUMO_{dipole}$–$HOMO_{dipolarophile}$-controlled 1,3-dipolar cycloadditions, i.e. **1** with **4**, **5** and **6**; **2** with **4** and **5**; **3** with **4**. Only in one case (reaction of **3** with **6**) the inverse $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction could be stated as the dominant one. Hammett's ρ-values and the solvent influence on the reaction rate are compatible with concerted cycloadditions.

Experimental

General: IR spectra were recorded with a Beckmann Acculab I—UV/VIS spectra and kinetics were recorded with a Zeiss Specord M 500, featuring an automatic changer for up to six 1-cm quartz cuvettes and a Colora MC 15 thermostat. For stopped-flow kinetics a Durrum D110 instrument with a Nicolet oscilloscope and a Colora thermostat was used.

UV/VIS and stopped-flow kinetics: Only pure azomethine ylides **1**–**3** were used. The stability of the dipoles in pure solvent without dipolarophile was monitored in an independent run parallel to the kinetic runs. The dipolarophiles **4**–**10** were pure (liquids >98%) compounds according to ^{1}H NMR and GC-analysis. All solvents used were highly purified according to standard procedures of the literature.

Separate solutions of pure dipoles **1**–**3** and pure dipolarophiles **4**–**10** were prepared in dry degassed 1,4-dioxane, acetonitrile or other pure dry solvents of Table 5. The concentration of the dipoles **1**–**3** was chosen to reach an extinction of approximately 1.0 in a 1-cm quartz cuvette after mixing in a 1:1 ratio with a solution of the dipolarophile in the same solvent (**1**–**3**: $c_o \times 10^4$=0.6–3.5 (mol l^{-1}). Dipolarophiles **4**–**10** were always used in a large excess according to its reactivity. Solutions containing **1**–**3** and **4**–**10** were pipetted into quartz cuvettes for

UV-measurements and thoroughly mixed. The progress of the reactions was followed by monitoring the $\pi-\pi^*$ transition of the dipoles at the absorption maxima in the corresponding solvent,[11,17–19] usually covering 10–90% of the reaction. All kinetic runs were always performed with two different concentrations of the dipolarophiles and at least duplicated once. The rate constants differed less than $\pm 3-4\%$ as a rule. Further experimental details for kinetic runs can be found in the literature.[17–19]

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