Thio- and Selenocarbonyl Compounds as “Superdienophiles” in [4+2] Cycloadditions☆

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Received May 22, 1998

Keywords: Cycloadditions / Substitution effects / Thiocarbonyl compounds / Selenocarbonyl compounds / Solvent effects

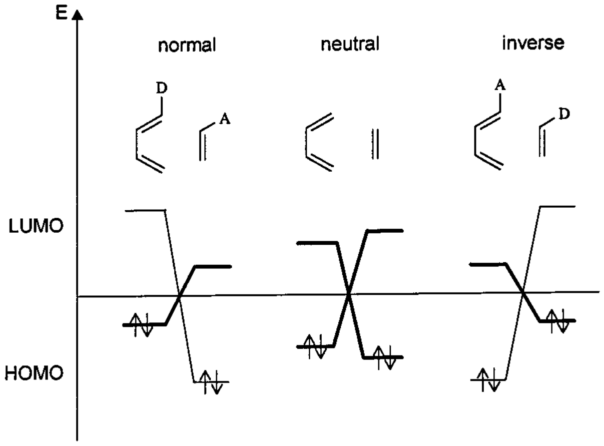
Normal, neutral, and inverse-type Diels–Alder reactions can be observed in [4+2] cycloadditions of thio- and selenocarbonyl compounds **1**–**9** with various cyclic and aryl-, methyl- or methoxy-substituted open-chain 1,3-butadienes. Extensive kinetic studies prove the highly dienophilic activity of the C=S and C=Se double bond. Studies of the solvent and temperature dependence of the reaction rate indicate a concerted mechanism.

Introduction

The Diels−Alder reaction is the most widely applied synthetic method for the formation of 6-membered carbocyclic and heterocyclic ring systems. Otto Diels and Kurt Alder were the first to understand the scope and importance of the so-called “diene synthesis”.[1][2][3][4] The “Alder rule” outlines the influence of electron donors (“activating ligands”) in the diene and electron acceptors in the dienophile. Both types of substituents accelerate the cycloaddition process.[5][6] Today this behavior is referred to as the Diels−Alder reaction with “normal electron demand”. Bachmann and Deno[7] first proposed the possibility of a reversal of the “normal” electronic properties and soon afterwards the Diels−Alder reaction following “inverse electron demand” was widely applied in synthesis[4][8] and verified by kinetic studies.[9] The normal and inverse mode of the [4+2] cycloaddition were completed by the Diels−Alder reaction with “neutral electron demand” which is looked upon as a transition between both types of reactivity.

An important milestone for the understanding of the Diels−Alder reaction were the Woodward−Hoffmann rules.[10] The FMO theory[11][12] considers only interaction between the HOMO and LUMO of diene and dienophile as the predominant interaction in the rate-determining transition state (Figure 1).

Figure 1. Classification of Diels−Alder reactions and orbital schemes



Houk et al.[13][14] proposed a very useful classification with regard to the nature of substituent. For quantitative treatments, substituent constants σ (Hammett)[15] or σ^+ (Brown)[16] have found widespread application in the empirically derived Hammett equation.[17] By application of Hammett′s model to the Diels−Alder reaction the following characteristic features can be found: Normal-electron-demand cycloadditions are characterized by a positive reaction constant ρ for the variation of substituents in the dienophile and negative ones for the variation of substituents in the diene. Therefore, electron acceptors (A) in the dienophile accelerate the reaction. Reversed ρ values are typical for inverse electron demand. In case of a cycloaddition reaction with neutral electron demand, typical “V”-shaped correlation plots of the kinetic data to substituent constants can be observed. Both types of substituents, electron-donating and -accepting groups, accelerate the cycloaddition process.

Besides concerted reaction pathways for the Diels−Alder reaction many biradical or zwitterionic mechanistic descriptions are rational. Since the influence of temperature and the surrounding solvent is important for stabilizing the transition state, studies of these effects are crucial to distinguish between various possible reaction pathways. Usually the influence of the solvent on the rate of Diels−Alder reactions is small if the process occurs concertedly. Solvent effects are less than a factor of 15 and a maximum of 70 for the rate constants in solvents of different polarity[18]

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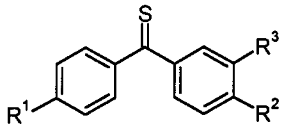
even though water is an exception to that general scheme. Due to hydrophobic interactions and increased hydrogen bonding to the activated complex, cycloaddition reactions in water are much faster than expected on the basis of solvent properties.[19][20][21][22][23][24][25][26] Various parameters, both theoretically and empirically derived, can be used to describe the solvent influence quantitatively. Well-known are E_T values (Dimroth and Reichardt),[18][27] donor[28] and acceptor numbers[29] (DN, AN). Other solvent parameters can be obtained from model systems proposed by Kosower (Z),[30] Hormadaly and Marcus (Z),[31] Brownstein (S),[32] Berson (Ω),[33] Nagai (D_Φ),[34] Winstein (Y),[35] Swain (Acidity, Basity)[36] and Catalan (SB)[37] as well as multiparameter approaches proposed by Koppel and Palm[38] or Kamlet and Taft.[39]

Thiones are known as "superdipolarophiles" as proven by Huisgen et al.[40] in the nitrone cycloaddition towards aliphatic thioketones.[41] Thiobenzophenone (**1a**) for instance reacts spontaneously with diazomethane even at −78°C.[42] Kinetic studies[43] for the reaction of diphenyldiazomethane with thiobenzophenone (**1a**) and thiofluorenone (**2**) showed the amazingly high reactivity of the C=S double bond in 1,3-dipolar cycloaddition reactions. The planar thiofluorenone (**2**) exceeds the reactivity of thiobenzophenone (**1a**) by two orders of magnitude. Since the mechanistic rational for the 1,3-dipolar cycloaddition and the Diels−Alder reaction is very similar one should also expect a high dienophilic character for the carbon−sulfur double bond. Since kinetic data for the reaction of C=S and C=Se bonds are scarce,[44] we want to report herein on extensive kinetic studies of the reactivity of sulfur− or selenium−carbon hetero double bonds towards a variety of substituted open-chain and cyclic 1,3-diene systems.

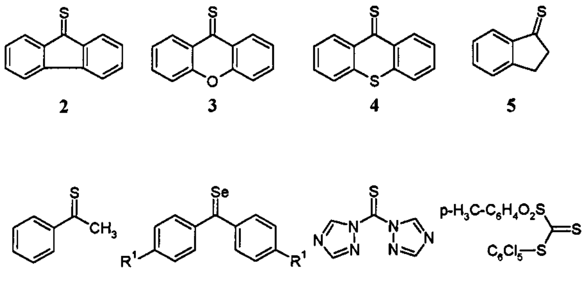
Results and Discussion

Due to the characteristic n−π* transition of the C=S double bond its cycloaddition reactions could be easily monitored by the disappearance of the distinctive colour of the C=X chromophor. Therefore, UV/Vis spectroscopy is the ideal tool to examine the reactivity of thio and seleno carbonyl compounds **1**−**9** (Figure 2) towards substituted 1,3-butadienes **10**−**17** (Figure 3). The course of each reaction studied kinetically has been determined by preliminary preparative experiments. Syntheses and purification of dienophiles **1**−**7**, dienes **10−17** and the resulting cycloadducts **18−39** have been described in detail in a previous publication.[45] The outcome of the kinetic runs was compared in every case by TLC and ^{1}H-NMR spectroscopy with the product of preparative runs, and no by-products could be detected. In all cases the reactions are standard second-order [4+2] cycloadditions, and conversions usually exceed 90%. The stability of thiones and selenones **1**−**9** was checked by UV/Vis monitoring of blank solutions. All dienophiles were stable under the chosen conditions when handled under an inert atmosphere in dry solvents.

Figure 2. Thiones **1**−**9** used in [4+2] cycloadditions



1	a	b	c	d	e	f	g
R¹	H	OCH₃	CH₃	CH₃	H	Cl	NO₂
R²	H	OCH₃	CH₃	H	H	Cl	H
R³	H	H	H	H	F	H	H



2 3 4 5

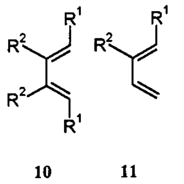
6 7 8 9

7	a	b	c
R¹	H	OCH₃	CH₃

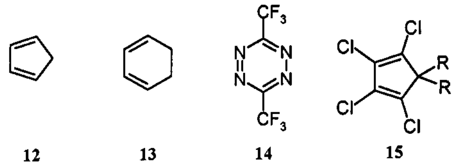
Reaction of Thiobenzophenone (1a) and Thiofluorenone (2) with 1,3-Dienes

Thiobenzophenone (**1a**) and thiofluorenone (**2**) were chosen initially since kinetic studies on the 1,3-dipolar reactivity of these thiones have been reported in the literature.[43] Furthermore, **1a** and **2** are easily accessible, stable and odourless compounds which show no tendency for enolization, a general problem with aliphatic thiocarbonyl compounds. Thiobenzophenone (**1a**) and thiofluorenone (**2**) react smoothly at room temperature in dichloromethane, which was chosen as solvent to enable direct comparison with data in the literature for the reaction of TCNE and maleic anhydride towards a full range of 1,3-butadienes.[2][46][47] Kinetic data have been collected for the [4+2] cycloadditions of thiones **1a** and **2** with methyl-, methoxy- and aryl-substituted 1,3-butadienes as well as 1,3-cyclopentadiene and 1,3-cyclohexadiene (Scheme 1) and are summarized in Table 1. The planar thiofluorenone (**2**) reacts about 200−20000 times faster than thiobenzophenone (**1a**) and in general the reactivity of **2** is as high as that of tetracyanoethylene (TCNE) and that of **1a** comparable with maleic anhydride.[2][46][47] With 1,3-butadiene (**10a**) thiofluorenone (**2**) reacts about 5 times faster than TCNE; in case of 1,3-cyclopentadiene (**12**) the reactivity of TCNE is about 700 times higher than that of **2**. If one compares thiobenzophenone (**1a**) with maleic anhydride as dienophile

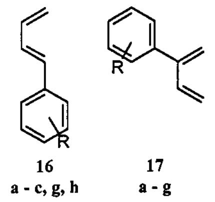
Figure 3. Open-chain and cyclic 1,3-dienes used in [4+2] cycloadditions



10/11	a	b	c	d	e	f
R^1	H	CH_3	H	H	OCH_3	Ph
R^2	H	H	CH_3	OCH_3	H	H



15	a	b	c	d	e
R	H	F	OMe	O-CH_2CH_2-O	Cl

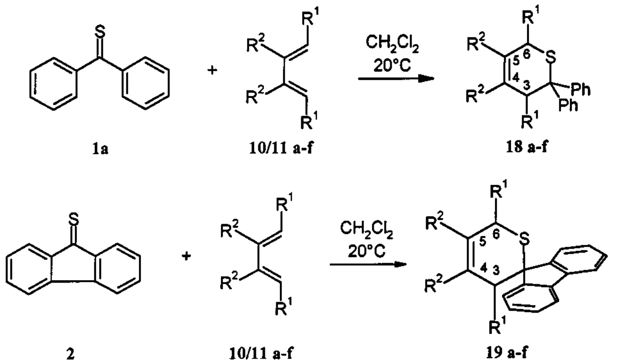


16/17	a	b	c	d	e	f	g	h
R	H	p-NMe_2	p-OMe	p-Me	m-F	m-Cl	m-CF_3	p-NO_2

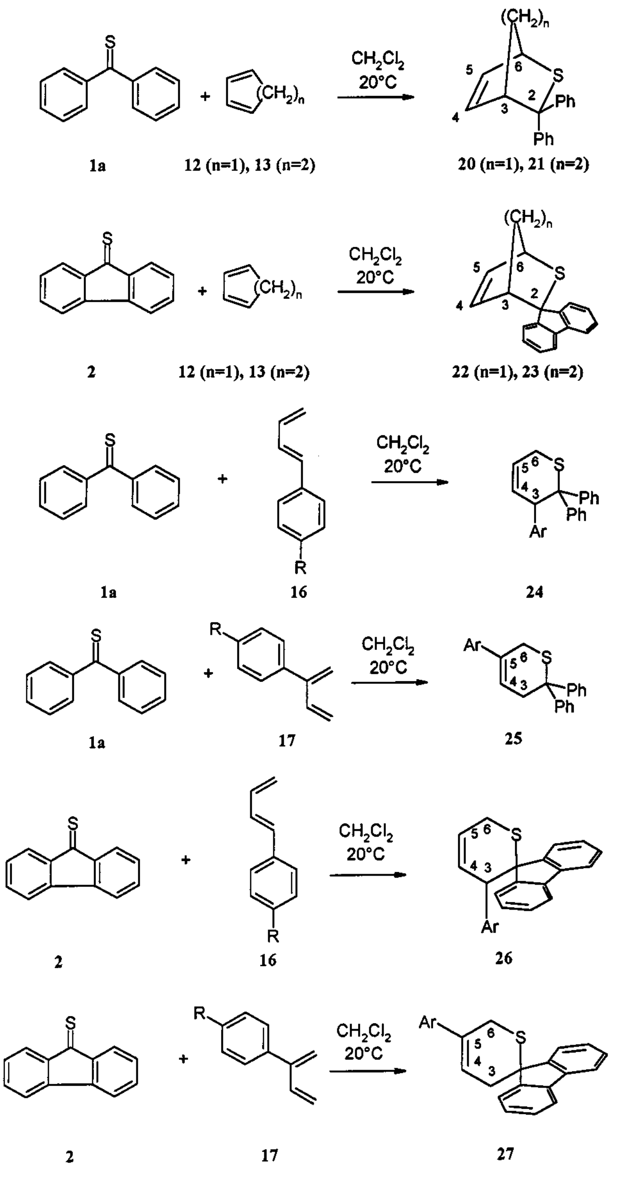
the reactivity ratios towards diene **10a** and **12** are 2 and 128, respectively, with a higher reactivity for maleic anhydride.

The difference in reactivity between both thiones is mainly due to steric interactions in the transition state: The planar thiofluorenone can be more easily approached by the 1,3-diene than thiobenzophenone (**1a**) in which both phenyl rings are about perpendicular as indicated by calculations (3-21G).[48] The correlation of the kinetic data of both thiones shows some interesting features (Figure 4). Only for simple methyl- and methoxy-substituted open-chain 1,3-dienes a linear relationship exists. 1- and 2-phenyl-1,3-butadiene deviated significantly from this linear correlation. In those cases different π-π interactions between the phenyl substituents and the planar system of fluorene might be the reason for a much higher reactivity. Despite those deviations some general features describe the [4+2] cycloaddition of **1a** and **2**. Butadienes with substituents in the 1-position react much faster than the corresponding 2-substituted dienes. The reactivity of dienes decreases from aryl to methoxy, methyl and hydrogen as the corresponding substituent. Comparison of the kinetic data of the thione addition to dienes with that of TCNE and maleic anhydride[2][46][47] indicates a similar mechanistic rational for both the C=S and C=C double bond but to gain further insight into the mechanistic pathways it is im-

Scheme 1. [4+2] Cycloadditions of thiones **1a** and **2** with open-chain and cyclic 1,3-dienes (CH_2Cl_2, 20°C)



10/11/18/19	a	b	c	d	e	f
R^1	H	CH_3	H	H	OCH_3	Ph
R^2	H	H	CH_3	OCH_3	H	H



16/17/24-27	a	b	c	d	e	f	g	h
R	H	p-NMe_2	p-OMe	p-Me	m-F	m-Cl	m-CF_3	p-NO_2

Table 1. Reaction of thiobenzophenone (**1a**) and thiofluorenone (**2**) with 1,3-dienes (20°C, CH_2Cl_2)

Diene	Thiofluorenone (**2**)		Thiobenzophenone (**1a**)	
	Range[a] [%]	$10^3\ k_2$ [$dm^3mol^{-1}s^{-1}$]	Range[a] [%]	$10^6\ k_2$ [$dm^3mol^{-1}s^{-1}$]
12	31−93 (11)	5120 ± 740	27−92 (4)	718 ± 32
16a	24−92(4)	2790 ± 270	1−96 (4)	603 ± 7
11e	20−92 (4)	2500 ± 260	16−98 (3)	129 ± 2.4
17a	14−98 (9)	1500 ± 90	1−96 (3)	7640 ± 196
10b	19−91 (13)	451 ± 31	1−89 (5)	109 ± 4.3
11b	24−90 (8)	291 ± 18	1−80 (4)	78.5 ± 1.8
10c	12−91 (12)	87.1 ± 8.2	22−84 (5)	68.3 ± 1.7
10f	3−90 (8)	44.9 ± 1.3	−	n.r.
11c	6−89 (8)	31.8 ± 0.9	23−80 (4)	50.8 ± 2.4
11d	13−78 (4)	11.4 ± 0.4	1−80 (4)	6.98 ± 0.99
10a	6−92 (4)	8.54 ± 0.45	1−90	33.2 ± 1.4
13	18−91 (6)	5.52 ± 0.27	−	−
10d	8−82 (8)	0.870 ± 0.09	−	n.r.

[a] Range of conversion followed by kinetic measurements. Number of independent runs in parentheses.

portant to study the influence of various substituents onto the reaction rate.

Substituent Dependence

For systematic studies of the influence of various substituents on the mechanism of [4+2] cycloaddition reactions the easily accessible (*E*)-1- and 2-aryl-1,3-butadienes **16/17** proved to be very useful probes.[49][50] The results of the kinetic measurements of the reaction of thiobenzophenone (**1a**) and thiofluorenone (**2**) with (*E*)-1- and 2-aryl-1,3-butadienes **16/17** are compiled in Tables 2, 7 and 8. Hammett plots for these investigations are shown in Figure 5 and 6. Correlation (cf. Table 2) of σ^+ values with $\log(k_R/k_H)$ give typical V-shaped curves for the reaction of thiones **1a** and **2** with (*E*)-1-arylbutadienes **16** indicating the relatively rare case of [4+2] cycloaddition reactions with neutral electron demand (Figure 5). Both donor and acceptor substituents in the 1,3-butadiene system lead to an increase in reactivity. Furthermore, the more reactive thiofluorenone (**2**) (5000 to 20000 times faster than thiobenzophenone depending on substituents in the 1,3-diene system) is more susceptible to slight changes in the electronic structure of the diene provoked by different substituents in the aryl moiety. Surprisingly, similar Hammett plots (Figure 6) for the reaction of thiones with 2-substituted aryl-1,3-butadienes show [4+2] cycloaddition with normal electron demand; electron-releasing substituents on the aryl moiety of the 1,3-dienes lead to higher reactivity towards thiones **1a** and **2**. Again the more reactive thiofluorenone (**2**) (in this case **2** is about 120 to 300 times more reactive than **1a**) shows a higher reaction constant with $\rho = -0.72$ relative to the small value of $\rho = -0.18$ for thiobenzophenone (**1a**). The seemingly minor variation from (*E*)-1- towards 2-substituted aryl-1,3-butadienes has a high impact on the electronic character of the [4+2] cycloaddition. Furthermore, 2-substituted arylbutadienes **17** react faster with thiobenzophenone (**1a**) than 1-substituted ones (**16**) ($k_{2\text{-aryl}}/k_{1\text{-aryl}}$ = 6−13) whilst this trend is reversed for thiofluorenone as dienophile ($k_{2\text{-aryl}}/k_{1\text{-aryl}}$ = 0.1−0.5).

Is it possible to change the electronic conditions of the reacting partners to such an extent as to arrive finally at Diels−Alder reactions of thiones following the inverse mode? For the attempt, 5,5-substituted 1,2,3,4-tetrachloro-1,3-cyclopentadienes[51][52] seem to be ideal. The reactivity of thiofluorenone (**2**) is high enough to give clean cycloadducts with polyhalogenated cyclopentadienes **15a−d** (Scheme 2).[45] Kinetic studies of these reactions were performed in dichloromethane at 20°C and the results are summarized in Table 9. As expected polyhalogenated cyclopentadienes **15a−d** react about 67 to 6700 times slower than 1,3-cyclopentadiene (**12**) with thiofluorenone (**2**), but reaction rates are in the same range as with cyclooctyne as dienophile but with different graduations of reactivity.[53] Diene **15a** (R = H) is the most reactive among the tested

Figure 4. Correlation of kinetic data for [4+2] cycloaddition of thioketones **1a** and **2** with various 1,3-dienes (20°C, CH_2Cl_2)

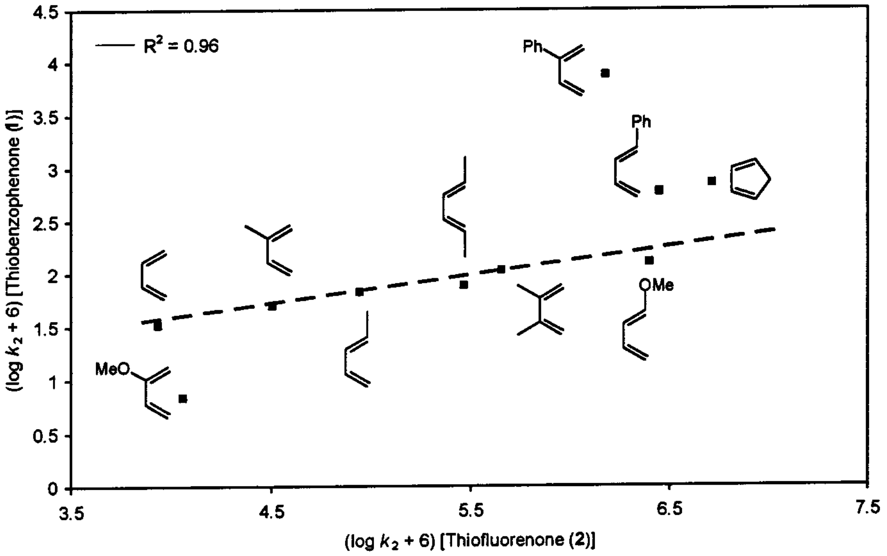


Figure 5. Correlation of kinetic data for [4+2] cycloadditions of thioketones **1a**, **2** and (*E*)-1-aryl-1,3-butadienes **16** with substituent constant σ^+ (20°C, CH_2Cl_2)

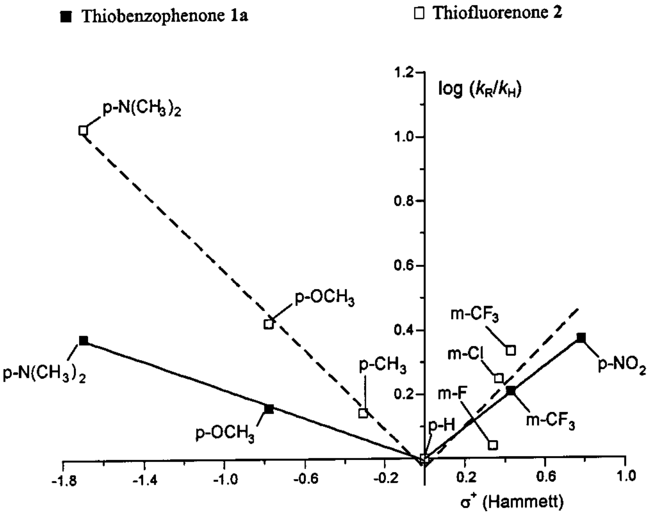
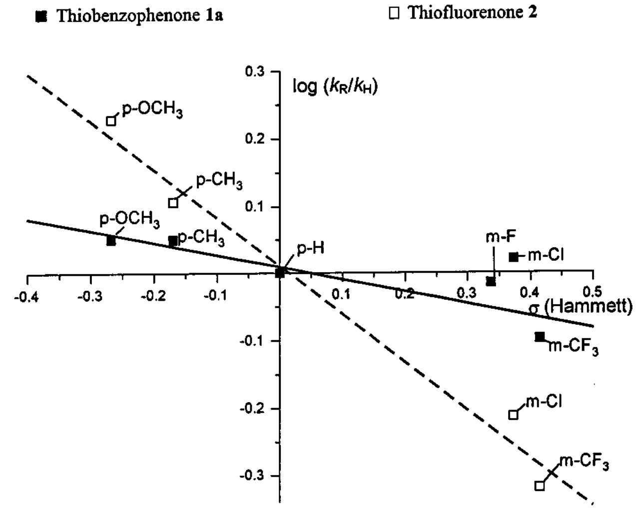
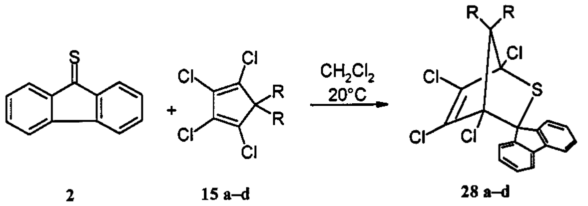


Figure 6. Correlation of kinetic data for [4+2] cycloadditions of thioketones **1a**, **2** and 2-aryl-1,3-butadienes **17** with substituent constant σ (20°C, CH_2Cl_2)



polyhalogenated cyclopentadienes. It reacts 99 times faster than **15c** (R = OMe). It is not possible to decide whether the [4+2] cycloadditions of thiofluorenone (**2**) with **15a–d** follow normal, neutral or inverse electron demand, since the sequence of the kinetic data does not fit into any of the standard schemes known for Diels–Alder reactions.

Scheme 2. [4+2] Cycloadditions of thiofluorenone (**2**) with tetrachlorinated 1,3-cyclopentadienes **15** (CH_2Cl_2, 20°C)



15/28	a	b	c	d
R	H	F	OMe	O-CH₂-

Substituted thiobenzophenones **1a–g** are ideal probes for studying the influence of different substituents in the 2π component of [4+2] cycloadditions (Scheme 3 and 4). The kinetic data for the reaction of substituted thiobenzophenones with diene **10c** and tetrazine **14** are compiled in Tables 2 and 10, Hammett plots of these reactions are shown in Figure 7. In case of disubstituted thiones, log (k_R/k_H) values are plotted against 2σ^+ values. Reaction constant $\rho = 2.4$ for the reaction with **10c** is quite high for concerted [4+2] cycloaddition reactions, but for the reaction of unsymmetrical dienophile this observation is well known.[54] The reactivity of thione **1a** to tetrazine **14** is very low relative to that of butadienes **10–17**. Therefore, these reactions were performed in toluene at 100°C. Plot of the kinetic data against σ or 2 σ clearly indicates a [4+2] cycloaddition with inverse electron demand ($\rho = -1.4$), a behaviour typical for 1,2,4,5-tetrazines in the Diels–Alder reaction.[55][56]

Reaction of Various Thio- and Selenocarbonyl Compounds with 2,3-Dimethyl-1,3-butadiene

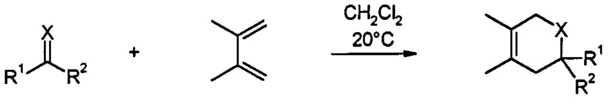
In addition to our systematic studies of the substituent dependence, various thio- and selenocarbonyl compounds were tested as dienophiles. All compounds **1–9** were tested against 2,3-dimethyl-1,3-butadiene (**10c**) (cf. Scheme 3); kinetic data for this approach are summarized in Table 3. Planarization of the thiobenzophenone system increases the reaction rate ($k_2/k_{1a} = 1300$). The high reactivity of thiofluorenone (**2**) can be lowered significantly by the incorporation of substituents in the planar system. Thioxanthione (**4**) and xanthione (**3**) exhibit a much lower reactivity

Table 2. Influence of substituents on the rate of [4+2] cycloadditions of various thiones and 1,3-dienes

Reaction of thione	with diene	electron demand	ρ_{Hammett}	σ values used	R[a]
1a	**16 a–c, g–h**	neutral	−0.63 0.48	σ^+	0.9995 0.9995
1a	**17 a, c–g**	normal	−0.18	σ	0.9090
2	**16 a–g**	neutral	−1.78 0.64	σ^+	0.9887 0.7563
2	**17 a, c–d, f–g**	normal	−0.72	σ	0.9890
1 a-d, f–g	**10c**	normal	2.40	σ	0.9885
1 a-c, e–g	**14**	inverse[b]	−1.40	σ	0.9939

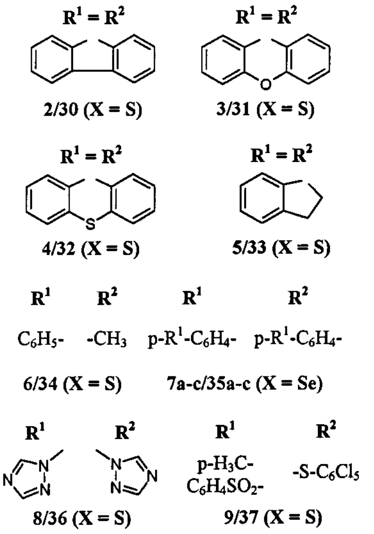
[a] Correlation coefficient for the linear regression analysis of the kinetic data (CH_2Cl_2, 20°C; toluene, 100°C for [b])

Scheme 3. [4+2] Cycloadditions of various thiones **1–9** with 2,3-dimethyl-1,3-butadiene (**10c**) (CH_2Cl_2, 20°C)



1 a - d, f, g, 2 - 9 **10c** **29 - 37**

1/29 (X = S)	a	b	c	d	f	g
R^1 p-C_6H_4-R^3; R^3	H	OCH_3	CH_3	CH_3	Cl	NO_2
R^2 p-C_6H_4-R^4; R^4	H	OCH_3	CH_3	H	Cl	H



2/30 (X = S) **3/31 (X = S)**

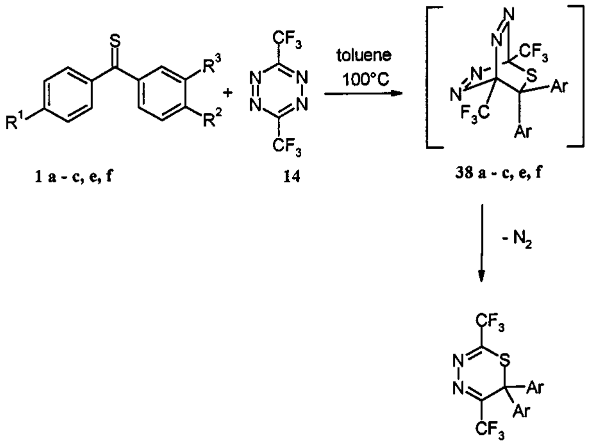
4/32 (X = S) **5/33 (X = S)**

6/34 (X = S) **7a-c/35a-c (X = Se)**

8/36 (X = S) **9/37 (X = S)**

7/35	a	b	c
R^1	H	OCH_3	CH_3

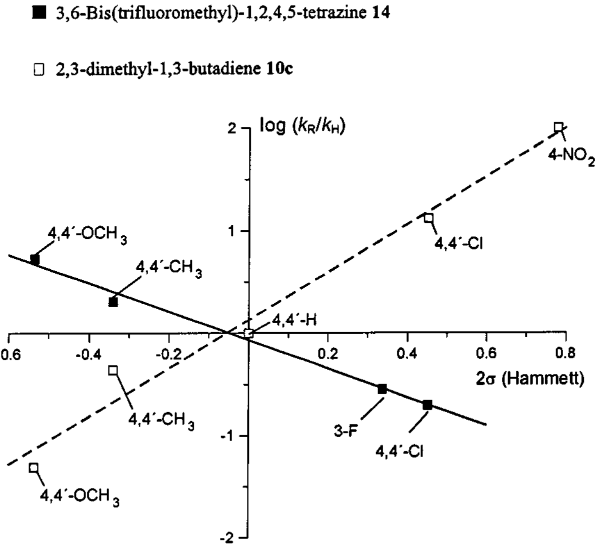
Scheme 4. [4+2] Cycloadditions of substituted thiobenzophenones **1** to 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (**14**) (toluene, 100°C)



1 a - c, e, f **14** **38 a - c, e, f** **39 a - c, e, f**

1/38/39	a	b	c	e	f
R^1	H	OCH_3	CH_3	H	Cl
R^2	H	OCH_3	CH_3	H	Cl
R^3	H	H	H	F	H

Figure 7. Correlation of kinetic data for [4+2] cycloadditions of thioketones **1** with 2,3-dimethyl-1,3-butadiene (**10c**) (CH_2Cl_2, 20°C) and 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (**14**) (toluene, 100°C) with substituent constant σ



towards 2,3-dimethyl-1,3-butadiene (**10c**) (k_2/k_4 = 1100 and k_2/k_3 = 89000) due to conjugative interactions of the donor heteroatom in the aromatic system and the C=S double bond. Electron-attracting substituents on the thiocarbonyl moiety lead to a significant increase in reactivity. Heterocyclic thione **8** reacts 13 times faster than the reference system **1a**. Substitution of a phenyl ring of **1a** by alkyl groups reduces the reaction rates. Thiobenzophenone (**1a**) reacts 2 times faster than **6** and 50 times faster than **5**. In both cases enolization to the corresponding thioenol is a significant side-reaction and destroys the dienophilic C=S moiety.

Table 3. Reaction of various thioketones with 2,3-dimethyl-1,3-butadiene (**10c**) (CH_2Cl_2, 20°C)

Thione	λ_{max} [nm]	Range[a] [%]	10^6 k_2 [$dm^3mol^{-1}s^{-1}$]	k_{rel}
1a	595	22–84 (5)	68.3 ± 1.7	≡ 1
2	446	12–91 (12)	87100 ± 8200	1300
3	409	6–67 (2)	0.974 ± 0.007	0.014
4	467	1–96 (4)	76.8 ± 0.7	1.1
5	539	2–75 (2)	1.5 ± 0.1	0.02
6	554	12–96 (4)	33.9 ± 0.3	0.50
7a	380	7–98 (12)	≈ 200 [b]	2.9
7b	700	1–94 (8)	32.7 ± 0.7	0.47
7c	718	7–92 (5)	254 ± 17	3.7
8	442	29–96 (4)	858 ± 6	13
9	522	20–96 (4)	585000 ± 12000	8600

[a] Range of conversion followed by kinetic measurments. Number of independent runs in parentheses. – [b] Measurement in benzene. The k_2 value was estimated with the assumption that the ratio[62] monomer/dimer is roughly 9:1 by the Bodenstein method as described in the literature.[63]

The higher homologues of the investigated thiones, the selenones **7a–c**,[62] react about 10 times faster than the corresponding compounds with C=S double bonds. Selenones with electron-accepting groups attached to the phenyl rings are instable compounds and tend to dimerize very quickly. Therefore, no kinetic studies with selenoketones with such substituents were possible, but the data obtained for **7a–c** indicate a concerted cycloaddition with normal (or neutral)

Table 4. Activation constants for the reaction of thiones **1a** and **2** with 2,3-dimethyl-1,3-butadiene (**10c**) (CH_2Cl_2, 20°C)

Thione	$\Delta H^{\neq}$ [kcal ·mol^{-1}]	$\Delta S^{\neq}$ [e.u.]
1a	13.5 ± 1.5	−32.0 ± 4.5
2	8.20 ± 0.6	−35.4 ± 2.2

electron demand. The reaction constant can be estimated $\rho \approx 0.6$ for the electron-releasing part of the Hammett plot. Dithioacid derivative **9**[57] exhibits the highest reactivity in the hetero Diels−Alder reaction of thiocarbonyl compounds we tested. It reacts 8600 times faster with **10c** than thiobenzophenone (**1a**), 6.6 times faster than thiofluorenone (**2**) and only 4.1 times slower than TCNE under the same conditions.

Temperature and Solvent Dependence

To gain deeper insight into the reactivity of thio- and selenocarbonyl compounds, the temperature and solvent dependence of the rate constants were determined for selected dienophiles. Activation enthalpy $\Delta H^{\neq}$ and entropy $\Delta S^{\neq}$[58] were determined for the reaction of thiobenzophenone (**1a**) and thiofluorenone (**2**) with diene **10c** in dichloromethane between 15 and 34°C (Tables 4 and 5). Especially the highly negative activation entropy is a very good indication for a highly pre-organized transition state for the thione [4+2] cycloaddition. Both activation enthalpy and entropy are in very good agreement with known examples of concerted Diels−Alder reactions indicating a reaction pathway similar to that for symmetrical dienophiles like TCNE and maleic anhydride.[2][46][47] Furthermore, Dondoni has measured the activation entropy $\Delta S^{\neq}$ (−27.8 e. u.) for the 1,3-dipolar cycloaddition of thiobenzophenone (**1a**) and 2,3,6-trimethylbenzonitrile *N*-oxide in CCl_4,[59] a value very similar to the one determined for the Diels−Alder reaction of **1a** with **10c**.

All kinetic data presented up to now indicate a concerted mechanism for the Diels−Alder reaction of thiones. To exclude the possibility of polar intermediates on the reaction pathway variation of solvent and determination of the corresponding reaction rates are useful tools since concerted [4+2] cycloaddition processes usually show little change in

Table 5. Temperature variation of the rate constants of thiobenzophenone (**1a**) and thiofluorenone (**2**) with 2,3-dimethyl-1,3-butadiene (**10c**) (CH_2Cl_2)

	1a			**2**	
T [°C]	Range[a] [%]	$10^6\ k_2$ [dm^{3}mol^{-1}s^{-1}]	*T* [°C]	Range[a] [%]	$10^2\ k_2$ [dm^{3}mol^{-1}s^{-1}]
30	10−95 (4)	150 ± 1	34	42−87 (4)	16.3 ± 0.4
25	7−97 (4)	108 ± 5	28	10−85 (4)	13.4 ± 0.5
15	10−93 (4)	51.4 ± 0.1	24	7−82 (5)	9.79 ± 0.5
			15	8−82 (3)	6.37 ± 0.13

[a] Range of conversion followed by kinetic measurements. Number of independent runs in parentheses.

Table 6. Influence of solvens on the rate constants for [4+2] cycloaddition of thiobenzophenone (**1a**) thiofluorenone (**2**) and 4,4′-dimethoxyselenobenzophenone (**7b**) with 2,3-dimethyl-1,3-butadiene (**10c**) (20°C)

	1a		**2**		**7b**	
Solvent	Range[a] [%]	$10^6\ k_2$·	Range[a] [%]	$10^2\ k_2$	Range[a] [%]	$10^6\ k_2$
n-C_6H_{12}	15−86 (4)	88.3 ± 2.6	13−89 (4)	4.10 ± 0.08	17−94 (4)	70.7 ± 4.7
toluene	24−85 (3)	83.7 ± 0.5	20−96 (4)	6.36 ± 0.04		
CH_2Cl_2	22−85 (5)	68.3 ± 1.7	12−90 (6)	8.71 ± 0.82	1−94 (8)	32.7 ± 0.7
1,4-dioxane	7−93 (4)	93.4 ± 1.0	17−97 (4)	10.9 ± 0.2		
H_3CCN	7−95 (4)	85.1 ± 1.0	18−86 (4)	15.5 ± 0.5	3−88 (4)	41.4 ± 0.5

[a] Range of conversion followed by kinetic measurements. Number of independent runs in parentheses.

Table 7. Reaction of thiofluorenone (**2**) with (*E*)-1- and 2-aryl-1,3-butadienes **16** and **17** (CH_2Cl_2, 20°C, λ_{max} = 446 nm)

		(*E*)-1-Aryl-1,3-butadienes **16**			(*E*)-2-Aryl-1,3-butadienes **17**	
No.	R	Range[a] [%]	k_2 [dm^{3}mol^{-1}s^{-1}]	No.	Range[a] [%]	k_2 [dm^{3}mol^{-1}s^{-1}]
16a	*p*-H	24−92 (4)	2.79 ± 0.27	**17a**	14−98 (9)	1.50 ± 0.09
16b	*p*-Me_2N	45−94 (4)	29.9 ± 6.6		−	−
16c	*p*-MeO	1−99 (18)	7.39 ± 1.52	**17c**	20−97 (4)	2.54 ± 0.29
16d	*m*-Me	24−93 (4)	3.88 ± 0.21	**17d**	18−97 (7)	1.92 ± 0.11
16e	*m*-F	29−97 (4)	3.06 ± 0.22		−	−
16f	*m*-Cl	20−99 (5)	4.93 ± 0.14	**17f**	12−95 (4)	0.92 ± 0.07
16g	*p*-F_3C	20−94 (3)	6.03 ± 0.28	**17g**	12−95 (4)	0.72 ± 0.02

[a] Range of conversion followed by kinetic measurements. Number of independent runs in parentheses.

Table 8. Reaction of thiobenzophenone (**1a**) with (*E*)-1- and 2-aryl-1,3-butadienes **16** and **17** (CH_2Cl_2, 20°C, λ_{max} = 595 nm)

		(*E*)-1-Aryl-1,3-butadienes **16**			(*E*)-2-Aryl-1,3-butadienes **17**	
No.	R	Range[a] [%]	10^6 k_2 [$dm^3mol^{-1}s^{-1}$]	No.	Range[a] [%]	10^6 k_2 [$dm^3mol^{-1}s^{-1}$]
16a	*p*-H	1−96 (4)	603 ± 7	**17a**	1−96 (3)	7640 ± 196
16b	*p*-Me_2N	11−92 (4)	1420 ± 19			
16c	*p*-MeO	26−96 (4)	858 ± 11	**17c**	21−96 (6)	8600 ± 140
				17d	21−95 (4)	8580 ± 100
				17e	21−96 (4)	7380 ± 41
				17f	13−97 (8)	8030 ± 140
16g	*m*-F_3C	24−95 (4)	962 ± 12	**17g**	18−96 (8)	6100 ± 220
16h	*p*-O_2N	27−93 (4)	1400 ± 41			

[a] Range of conversion followed by kinetic measurements. Number of independent runs in parentheses.

reactivity with solvent variation.[2][18] Rate constants for the Diels−Alder reactions of thiobenzophenone (**1a**), thiofluorenone (**2**) and 4,4′-dimethoxyselenophenone (**7b**) with 2,3-dimethyl-1,3-butadiene (**10c**) at 20°C are compiled in Table 6. In all three cases only slight effects of solvents on the reaction rates could be determined. Thiobenzophenone (**1a**) shows almost no solvent dependence in the five solvents chosen. In case of thione **2** a slight increase of the *k* values with increasing solvent polarity is observed. In acetonitrile the reaction is about 3.8 times faster than in nonpolar media like *n*-hexane. Surprisingly, an inverse trend can be observed for selenocarbonyl compound **7b**. Amongst the three solvents tested the less polar solvent *n*-hexane seems to be the best medium for the hetero Diels−Alder reaction but the observed effects are rather small (2.16 relative to dichloromethane).

Table 9. Reaction of 5,5-disubstituted 1,2,3,4-tetrachloro-1,3-cyclopentadienes **15** with thiofluorenone (**2**) (CH_2Cl_2, 20°C, λ_{max} = 446 nm)

Diene	R	Range[a] [%]	10^3 k_2 [$dm^3mol^{-1}s^{-1}$]
15a	H	14−97 (6)	75.9 ± 2.8
15b	F	15−90 (4)	6.01 ± 0.13
15c	MeO	25−89 (4)	0.766 ± 0.076
15d	OCH_2CH_2O	8−90 (4)	8.54 ± 0.10
15e	Cl	−	n.r.

[a] Range of conversion followed by kinetic measurements. Number of independent runs in parentheses.

Conclusions

The result of this study confirm the high reactivity of thio- and selenocarbonyl compounds as dienophiles in [4+2] cycloaddition reactions. Despite the low symmetry of these dienophiles it could be proven by systematic investigation of the influence of substituents, solvents and temperature on the Diels−Alder reactions that all reactions follow a concerted reaction pathway. Furthermore, all cases of electron demand (normal, neutral and inverse) in the [4+2] cycloaddition could be observed and the reactivity of some thiones (e. g. **2** and **9**) are surprisingly high indicating their *superdienophilic* character.

We are grateful to the *Deutsche Forschungsgemeinschaft* (DFG) , the *Fonds der Chemischen Industrie*, and the *BASF AG*, Ludwigshafen/Rhein, for financial support of this investigation.

Experimental Section

Thio- and seleno carbonyl compounds **1−7** and **9** and dienes **10−17** were synthesized and purified as outlined in a previous paper.[45][60][61] − UV/Vis: Kinetic measurements were performed using a Zeiss Specord M400 spectrometer with a WTM M8 thermostat or a Zeiss PMQ II spectrometer with a Colora thermostat, both systems featuring an automatic charger for four or six quartz cuvettes. − Stopped-flow: Kinetic data were recorded using a Durrum D 110 instrument with a Nicolet oscilloscope and a Colora thermostat. The stopped-flow technique was used in case of reactions with $k_2 > 10$ dm^3 $mol^{-1}s^{-1}$.

UV/Vis and Stopped-Flow Kinetic Measurements: Separate solutions of pure thio or seleno carbonyl compounds **1−9** and dienes

Table 10. Reaction of substituted thiobenzophenones **1** with 2,3-dimethyl-1,3-butadiene (**10c**) (20°C, CH_2Cl_2) and 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (**14**) (100°C, toluene)

Thione			Butadiene **10c**		Tetrazine **14**	
No.	R	λ_{max} [nm]	Range[a] [%]	10^6 k_2 [$dm^3mol^{-1}s^{-1}$]	Range[a] [%]	10^6 k_2 [$dm^3mol^{-1}s^{-1}$]
1a	4,4′-H	595	22−84 (5)	68.3 ± 1.7	1−72 (2)	572 ± 6
1b	4,4′-$(MeO)_2$	575	4−89 (7)	3.35 ± 0.18	2−83 (2)	3045 ± 27
1c	4,4′-Me_2	587	4−90 (4)	14.5 ± 0.3	5−78 (2)	1155 ± 33
1d	4-Me	593	1−90 (8)	30.0 ± 1.2	−	−
1e	3-F	604	−	−	8−62 (2)	162 ± 3
1f	4,4′-Cl_2	598	12−90 (4)	908 ± 33	13−64 (2)	113 ± 1
1g	4-O_2N	610	22−97 (5)	6850 ± 300	−	−

[a] Range of conversion followed by kinetic measurements. Number of independent runs in parentheses.

10−17 were prepared in degassed, dry solvent at the temperature used for the kinetic run. The stability of **1−9** was checked by UV/Vis monitoring of its longest wavelength absorption maximum. Solutions containing $3-9 \times 10^{-3}$ mol l^{-1} of **1−9** and a 1- to 50-fold excess of dienes were pipetted into quartz cuvettes for UV measurement or united by high-speed injection in stopped-flow experiments. The reaction progress was followed to completion by monitoring the n-π^* transition of the dienophile to cover usually 10−90% of the reaction.

In case of 1,3-butadiene (**10a**) as 4-π component it was not possible to determine the concentration of stock solution by weighing. Therefore, a fast and reliable titration method was developed: 1,3-Butadiene (**10a**) gas was condensed into ampoules, the amount of diene was roughly determined by weighing and then was transferred into a known amount of solvent in this way yielding a stock solution of 1,3-butadiene (**10a**) of about 0.1 mol l^{-1} concentration. The exact contents of these solutions were determined by titration with a known amount of 4-methyl-1,2,4-triazoline-2,5-dione. Stock solutions of 1,3-butadiene (**10a**) in dichloromethane ($c = 0.07$ to 0.1 mol dm^{-1}) are stable up to 2 d at room temperature.

General: Values for k_2 from all measurements were obtained using linear least-squares computer simulation for second- or pseudo-first-order reactions, and parallel runs (4−10) were carried out to reproduce the rate constats within ± 5% or better.

☆ Dedicated to Professor *Heinrich Nöth* on the occasion of his 70th birthday.

[1] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98−122.
[2] J. Sauer, R. Sustmann, *Angew. Chem.* **1980**, *92*, 773−801; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779−807.
[3] J. Hamer *1,4-Cycloaddition Reactions*, Academic Academic Press, New York, **1967**.
[4] D. L. Boger, N. Weinreb in *Hetero-Diels−Alder Methodology* (Ed.: H. Wassermann), Academic Press, New York, **1987**, vol. 47.
[5] J. Sauer, H. Wiest, A. Mielert, *Chem. Ber.* **1964**, *67*, 3183−3207.
[6] J. Sauer, D. Lang, H. Wiest, *Chem. Ber.* **1964**, *67*, 3208−3218.
[7] W. E. Bachmann, N. C. Deno, *J. Am. Chem. Soc.* **1949**, *71*, 3062−3072.
[8] R. A. Carboni, R. V. J. Lindsey, *J. Am. Chem. Soc.* **1959**, *81*, 4342−4346.
[9] J. Sauer, H. Wiest, *Angew. Chem.* **1962**, *74*, 353; *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 269.
[10] R. B. Woodward, R. Hoffmann, *Angew. Chem.* **1969**, *81*, 797−869; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781−853.
[11] R. Sustmann, *Pure Appl. Chem.* **1974**, *40*, 569−593.
[12] K. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57−64.
[13] K. N. Houk, *J. Am. Chem. Soc.* **1973**, *95*, 4092−4094.
[14] K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7301−7315.
[15] O. Exner in *Correlation Analysis in Chemistry* (Eds. N. B. Chapman, J. Shorter), Plenum Press, New York, **1978,** p. 439.
[16] H. C. Brown, Y. Okamoto, T. Inukai, *J. Am. Chem. Soc.* **1958**, *80*, 4964−4968.
[17] L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 69−103.
[18] C. Reichardt, *Solvent and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, Weinheim, **1988**, p. 121ff.
[19] D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 1816−7817.
[20] A. Lubineau, *J. Org. Chem.* **1986**, *51*, 2142−2144.
[21] P. A. Grieco, *Aldrichim. Acta* **1991**, *24*, 59−66.
[22] J. B. F. N. Engberts, *Pure Appl. Chem.* **1995**, *67*, 823−828.
[23] J. W. Wijnen, J. B. F. N. Engberts, *Liebigs Ann.* **1997**, 1085−1088.
[24] J. Sauer, F. Schuster, R. Braun, *Tetrahedron Lett.* **1986**, *27*, 1285−1288.
[25] C. J. Li, T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley and Sons, New York, **1997**.
[26] *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie Academic and Professional, London, **1998**.
[27] K. Dimroth, C. Reichardt, T. Siepmann, F. Bohlmann, *Justus Liebigs Ann. Chem.* **1963**, *661*, 1−37.
[28] V. Gutmann, E. Wychera, *Inorg. Nucl. Chem. Lett.* **1966**, *2*, 257−260.
[29] V. Gutmann, U. Mayer, W. Gerger, *Monatsh. Chem.* **1975**, *106*, 1235−1257.
[30] E. M. Kosower, *J. Am. Chem. Soc.* **1958**, *80*, 3253−3260.
[31] J. Hormadaly, Y. Marcus, *J. Phys. Chem.* **1960**, *38*, 1590−1596.
[32] S. Brownstein, *Can. J. Chem.* **1960**, *38*, 1590−1596.
[33] J. A. Berson, Z. Hamlet, W. A. Mueller, *J. Am. Chem. Soc.* **1962**, *84*, 297−304.
[34] T. Oshima, S. Arikata, T. Nagai, *J. Chem. Res. (S)* **1981**, 204−205.
[35] S. Winstein, S. G. Smith, A. H. Fainberg, *J. Am. Chem. Soc.* **1961**, *83*, 618−625.
[36] C. G. Swain, M. S. Swain, A. L. Powell, S. Alunni, *J. Am. Chem. Soc.* **1983**, *105*, 502−513.
[37] J. Catalan, C. Diaz, V. Lopez, P. Perez, J.-L. G. de Paz, J. G. Rodriguez, *Liebigs Ann.* **1996**, 1785−1794.
[38] I. A. Koppel, V. A. Palm in *Advances in Linear Free-Energy Relationships* (Eds: N. B. Chapmann, J. Shorter), Plenum, London, **1972**, p. 203.
[39] M. J. Kamlet, M. E. Jones, R. W. Taft, *J. Chem. Soc., Perkin Trans. 2* **1979**, 349−356.
[40] R. Huisgen, L. Fisera, H. Giera, R. Sustmann, *J. Am. Chem. Soc.* **1995**, *117*, 9671−9678.
[41] R. Huisgen, H. Giera, *Liebigs Ann.* **1997**, 1685−1689.
[42] R. Huisgen, X. Li, *Tetrahedron Lett.* **1983**, *24*, 4185−4188.
[43] R. Huisgen, E. Langhals, *Tetrahedron Lett.* **1989**, *30*, 5369−5372.
[44] J. Schatz, J. Sauer, *Tetrahedron Lett.* **1994**, *35*, 4767−4770.
[45] J. Breu, P. Höcht, U. Rohr, J. Schatz, J. Sauer, *Eur. J. Org. Chem.* **1998**, 2861−2873.
[46] J. Drexler, M. A. Lindermayer, M. A. Hassan, J. Sauer, *Tetrahedron Lett.* **1985**, *26*, 2559−2562.
[47] C. Rücker, D. Lang, J. Sauer, H. Friege, R. Sustmann, *Chem. Ber.* **1980**, *113*, 1663−1690.
[48] R. Sustmann, private communication.
[49] J. Drexler, Ph. D. Dissertation, University of Regensburg, **1984**.
[50] H. Adam, Ph. D. Dissertation, University of Regensburg, **1994**.
[51] E. Eibler, T. Burgemeister, P. Höcht, B. Prantl, H. Roßmaier, H. Schuhbauer, H. Wiest, J. Sauer, *Liebigs Ann.* **1997**, 2451−2469.
[52] E. Eibler, P. Höcht, B. Prantl, H. Roßmaier, H. Schuhbauer, H. Wiest, J. Sauer, *Liebigs Ann.* **1997**, 2471−2484.
[53] P. Höcht, Ph. D. Dissertation, University of Regensburg, **1994**.
[54] J. Hamer, M. Ahmad, *J. Org. Chem.* **1966**, *31*, 2829−2833.
[55] J. Sauer, *Bull. Soc. Chim. Belg.* **1992**, *101*, 521−540.
[56] J. Sauer in *1,2,4,5-Tetrazines* (Eds.: Ch. W. Rees, A. J. Boulton, A. R. Katritzky), Pergamon Press, Oxford, **1996**, vol. 6, p. 901.
[57] I. El-Sayed, M. F. Abdel-Megeed, S. Yassin, A. Senning, *Sulfur Lett.* **1992**, *15*, 1−4.
[58] H. Eyring, *Chem. Rev.* **1935**, *17*, 65−79.
[59] A. Battaglia, A. Dondoni, G. Maccagnani, G. Mazzant, *J. Chem. Soc. B* **1971**, 2096−2100.
[60] J. Schatz, Ph. D. Dissertation, University of Regensburg, **1994**.
[61] U. Rohr, Ph. D. Dissertation, University of Regensburg, **1996**.
[62] G. Erker, F.-G. Klärner, R. Hock, C. Krüger, S. Werner, U. Artschwanger-Perl, *Angew. Chem.* **1990**, *102*, 1082−1084; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1067−1069.
[63] R. Huisgen, *Pure Appl. Chem.* **1989**, *61*, 613−628.

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