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STRUCTURE–REACTIVITY PROBLEM IN CYCLOADDITION REACTIONS TO FORM HETEROCYCLIC COMPOUNDS

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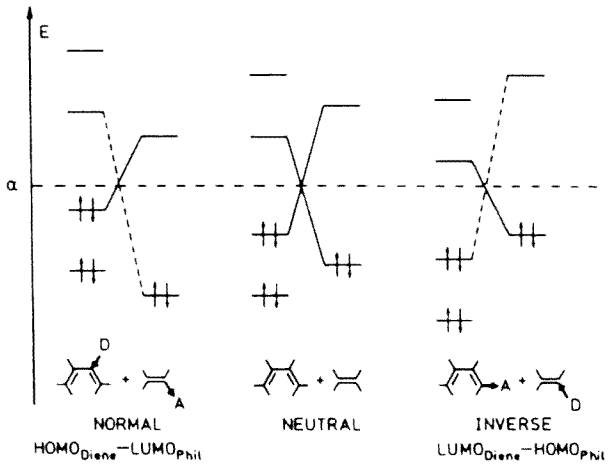
The steric and electronic effects of substituents in both diene and dienophile components have been considered as the main factors that control the electronic character of (4+2)-cycloaddition leading to transitions between "normal," "neutral," and "inverse" Diels–Alder reactions.

Cycloaddition reactions still prove to be one of the most important tools in synthetic organic chemistry. The ring size of the cycloadducts formed ranges from three to six-membered rings, which can be obtained in stereospecific and highly regioselective reactions. Using the intramolecular variant and changing from CC to hetero 4π- and 2π-systems bicyclic and polycyclic carbocycles and heterocycles can be synthesized [1, 2].

Limiting the discussion to (4+2)-cycloadditions, the simple FMO-picture developed by Fukui and Sustmann tells us which variations we have to expect in principle when we substitute the 4π-system (diene) and the 2π-system (dienophile).



Scheme 1. Orbital arrangement for normal, neutral, and inverse Diels–Alder reactions.

The second case in Scheme 1 shows the symmetrical arrangement of both HOMO–LUMO interactions representing the neutral case of Diels–Alder reactions, which is rather rare. Any exchange of hydrogen against donor or acceptor substituents in diene or dienophile increases the rate. At the left side, caused by donors in the diene and acceptors in the dienophile, we find the normal case ($HOMO_{diene}-LUMO_{phil}$-control), predicted early by Alder's rule [3]. Finally the reverse case, the inverse type Diels–Alder reaction, is symbolized by the $LUMO_{diene}-HOMO_{phil}$-control caused now by acceptors in the diene and donors in the dienophile.

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TABLE 1. Rate Data for (4+2)-Cycloaddition Reactions of Cyclic Dienophiles with 1,2,4,5-Tetrazine

Reaction with  , $10^7 \cdot k_2$ [l/mol · s], 20°C, dioxane

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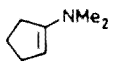
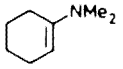
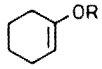
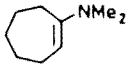
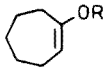
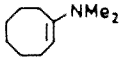
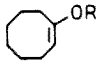
	27 600	 100 000 000	 344 244
	275	 2 160 000	 1.7 1.4
	35 900	 68 300 000	 1 190 1 220
	57 500	 214 000 000	 1 260 513

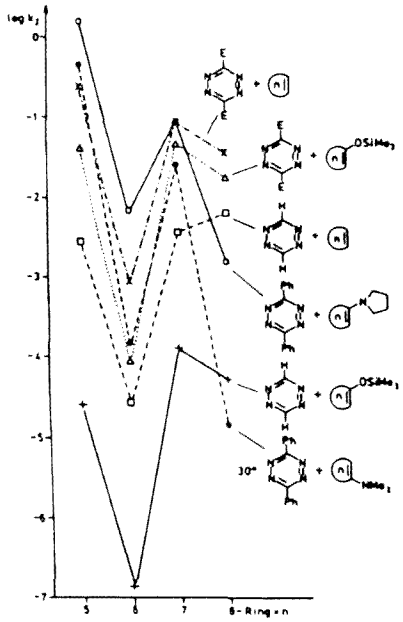
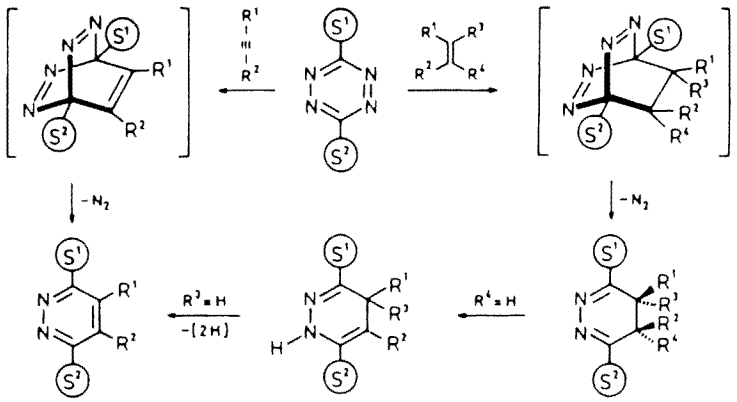


Fig. 1. Dependence of log k [$l \cdot mol^{-1} \cdot s^{-1}$] for (4+2)-cycloaddition reactions of cyclic dienophiles with 1,2,4,5-tetrazines from ring size of the dienophiles (reactions in dioxane, 20°C).

This last case was predicated by Bachmann and Deno as early as 1949 [4]. As the model system chosen was inappropriate, the idea was forgotten for more than 10 years until Carboni and Lindsey, of the DuPont group, published unexpected reactions of 1,2,4,5-tetrazines with simple olefins [5]; the Diels–Alder scheme was a suitable way to explain the product structure. Finally, our first kinetic studies proved these reactions to be of inverse type Diels–Alder reactions [6].

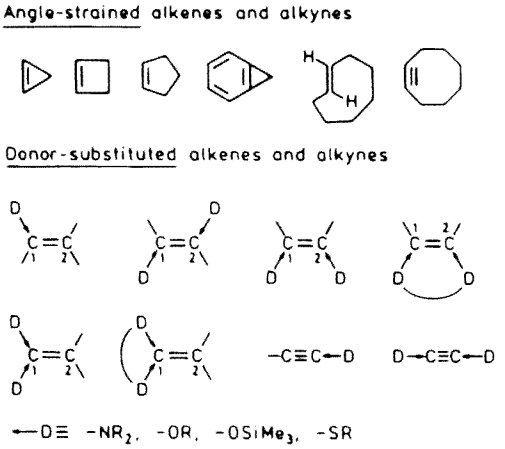
The general scheme for these (4+2)-cycloadditions of 1,2,4,5-tetrazines is well known to most of the chemists in the field of heterocyclic chemistry (Scheme 2). The initial cycloaddition step with alkenes or alkynes forms bicyclic Diels–Alder adducts, never isolated because of extremely rapid nitrogen loss with activation enthalpies between almost zero and a few kcal/

mol according to *ab initio* calculations [7]. The reaction sequence finally yields pyridazines and/or dihydropyridazine tautomers. The same mechanistic scheme is also valid for 1,2,4-triazines as starting dienes leading to pyridine or dihydropyridine derivatives. According to mechanistic studies the initial step is a symmetry-allowed concerted (4+2)-cycloaddition.



Scheme 2. (4+2)-Cycloaddition reactions of 1,2,4,5-tetrazines with alkenes and alkynes.

Until now organic chemistry textbooks have still ignored this reaction type. Until now TCNE and maleic anhydride, for instance, are regarded to be the record dienophiles. According to a wealth of kinetic data already published [8-10] we know that the combination of donor substituted open chain and cyclic alkenes and alkynes with electron deficient heterocycles brings the rate constant up to those of diffusion controlled reactions (Scheme 3). The angle strain which is partly lost in the transition state of the cycloaddition step, thus lowering the activation barrier, also increases the reaction rate considerably, as will be shown later.

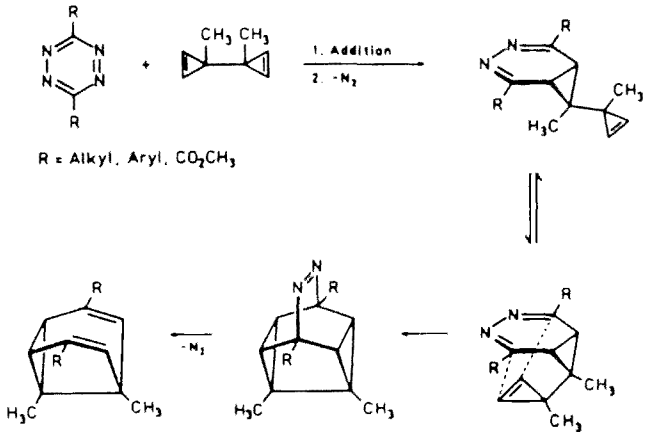


Scheme 3. Dienophiles suitable for (4+2)-cycloaddition reactions to 1,2,4,5-tetrazines: angle-strained and donor-substituted alkenes and alkynes.

Let me sketch only briefly the synthetic value of the tetrazine and triazine cycloaddition reactions and illustrate this with a few schemes.

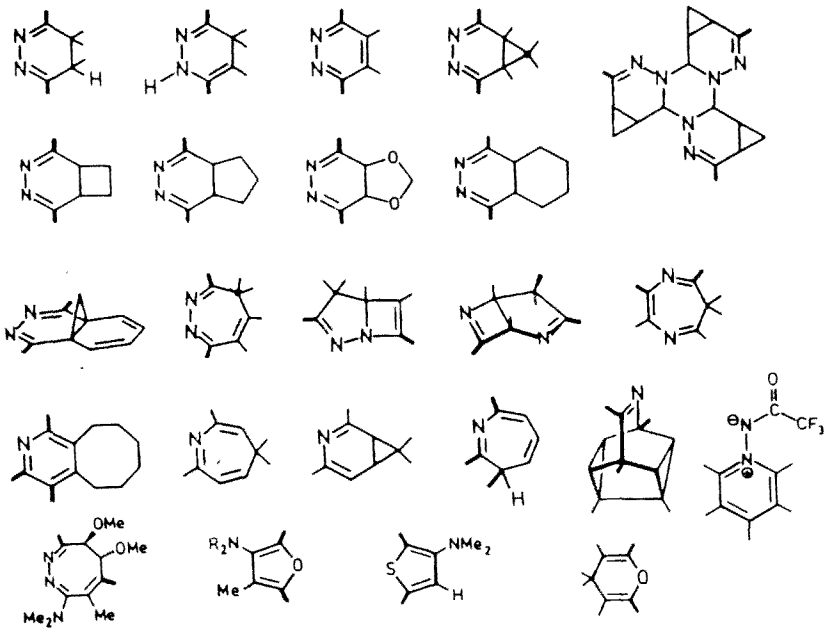
Cyclopropenes turned out to be dienophiles leading to complicated structures in a few steps sometimes in one-pot reactions. Bicyclopropenyl, for instance, may show this as an example (Scheme 4). The first cycloaddition–cycloelimination sequence shows that diazanorcaradienes are available by this route in principle, a class of compound undergoing rapid valence isomerization, in this way bringing the second cyclopropene unit in a syn-arrangement with regard to the heterodiene system, suitable for a second, now intramolecular (4+2)-cycloaddition to form a polycyclic azo compound, a second structure type

easily available by these cycloaddition reactions of six-membered heterocycles. Finally, thermal or photochemical nitrogen elimination from azo compounds formed leads to carbocycles, here semibullvalene derivatives [11-13].

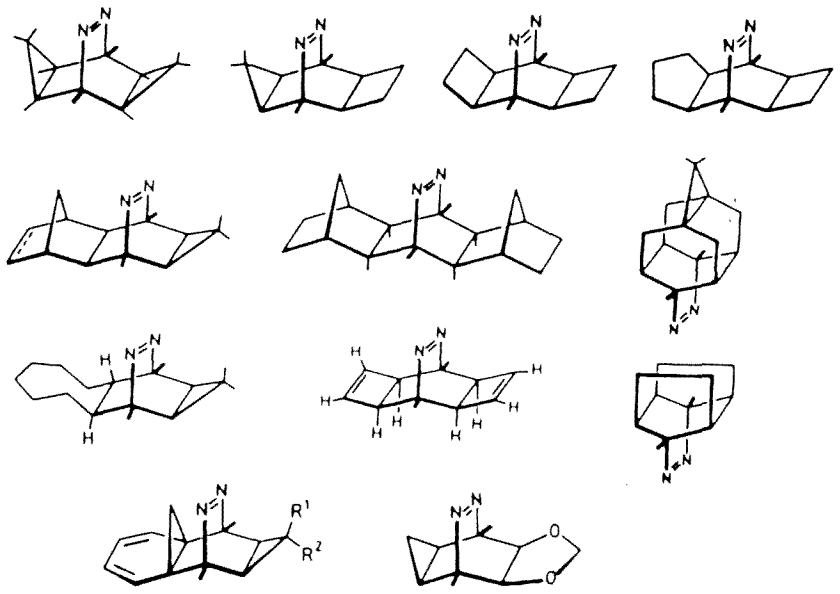


Scheme 4. Tandem reaction of a bicyclopropenyl derivative with 1,2,4,5-tetrazines.

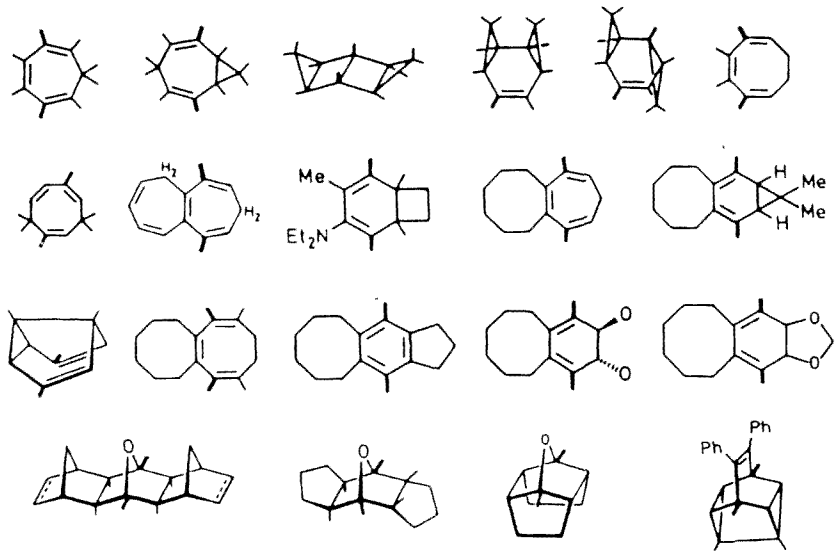
Summarizing, diaza heterocycles, azo compounds, and carbocycles are the principal structural types available by these inverse type Diels–Alder reactions of six-membered heterocycles. Three schemes only give us a survey and should illustrate this idea in principle showing structures which are products of the cycloadditions discussed (Schemes 5, 6, 7).



Scheme 5. Heterocyclic compounds available through (4+2)-cycloaddition reactions of electron-poor heterocyclic 4π-systems.



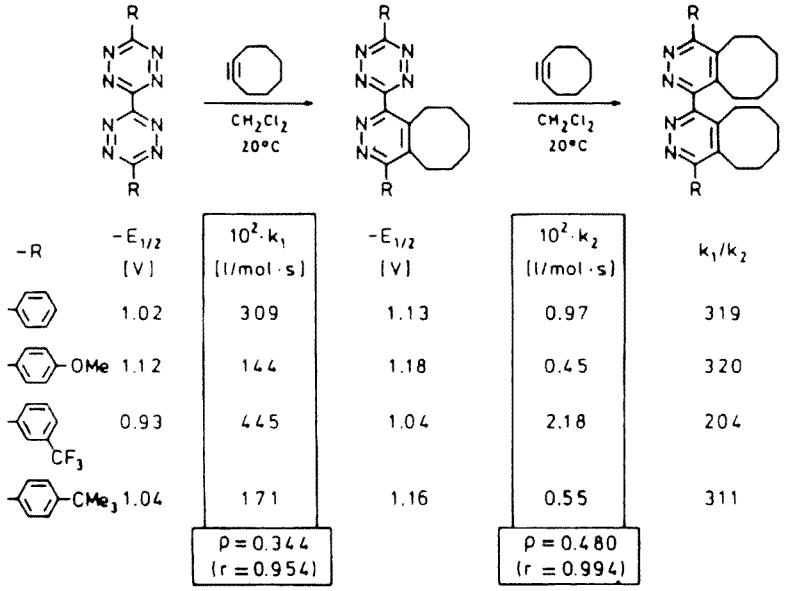
Scheme 6. Polycyclic azo compounds available through (4+2)-cycloaddition reactions of 1,2,4,5-tetrazines with two equivalents of alkenes.



Scheme 7. Carbocyclic compounds obtained from azo compounds by loss of nitrogen.

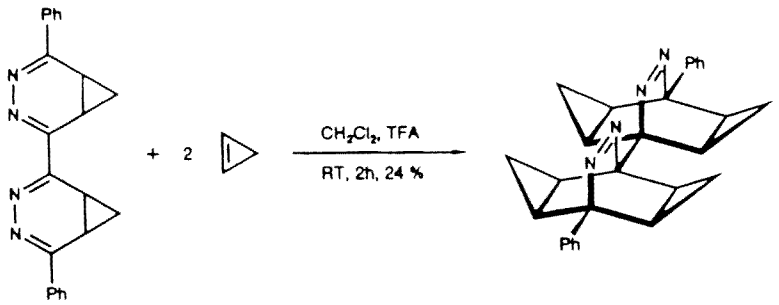
Some new synthetic aspects are presented with respect to a few examples of bi- and trifunctional tetrazines and triazines as starting compounds in these cycloadditions.

Quite recently we succeeded in synthesizing bitetrazines and bitriazines and using these bifunctional heterocyclic 4π-systems as dienes [14]. The diarylbitetrazines react as bifunctional tetrazines with a difference in rate constants by a factor of 200-320 between the first and the second step (Scheme 8). Bifunctional diazanorcaradienes can be transformed to bisadducts (Scheme 9) and homotropilidenes (Scheme 10). The corresponding triazines (Scheme 11) open the way to interesting polyaryls which might be of value as complexing agents in the case of the polypyridine derivative. The bistetrazolotetrazine reacts readily with cyclooctyne; the pyridazine formed now can react with carboxylic acid derivatives transforming the starting compound to linear polyheterocycles by transformation of the tetrazole ring (Scheme 12) [15, 16].

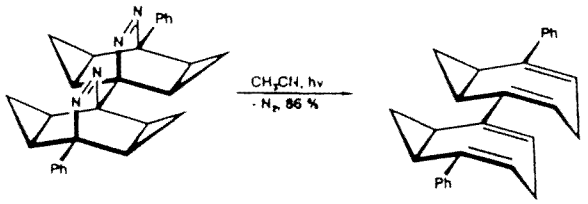


-R	$-E_{1/2}$ [V]	$10^2 \cdot k_1$ [l/mol·s]	$-E_{1/2}$ [V]	$10^2 \cdot k_2$ [l/mol·s]	k_1/k_2
Ph	1.02	309	1.13	0.97	319
p-OMeC6H4	1.12	144	1.18	0.45	320
p-CF3C6H4	0.93	445	1.04	2.18	204
p-CMe3C6H4	1.04	171	1.16	0.55	311
		ρ = 0.344 (r = 0.954)		ρ = 0.480 (r = 0.994)	

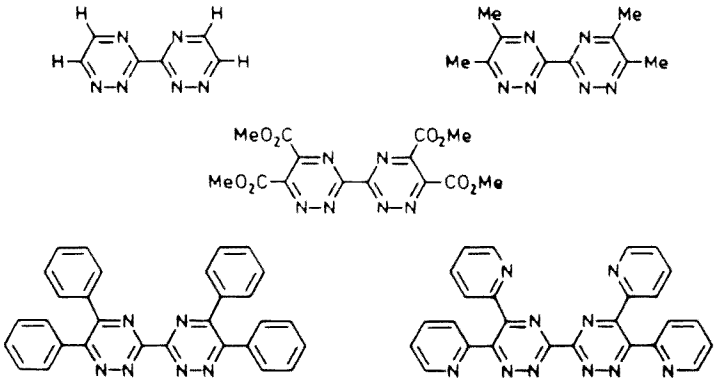
Scheme 8. Reaction of bitetrazines with cyclooctyne.



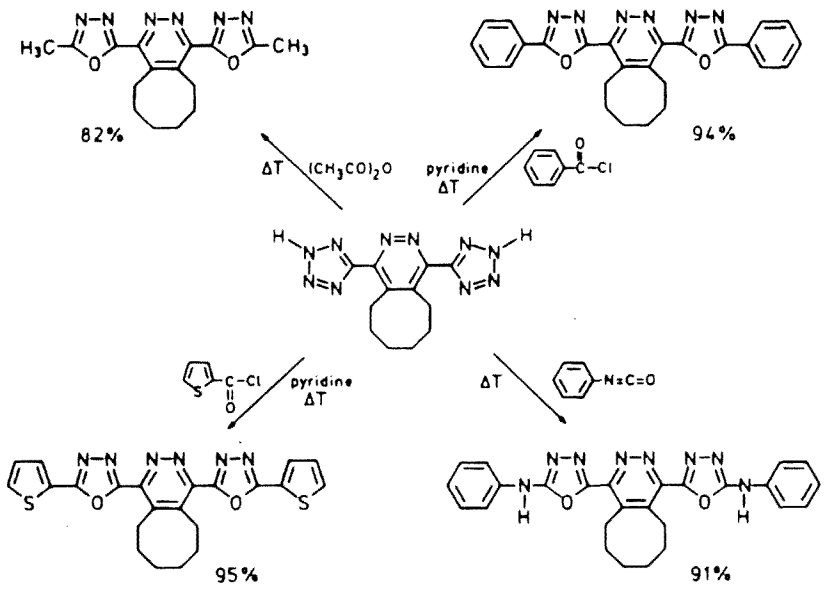
Scheme 9. Reaction of a bifunctional diazanorcaradiene with cyclopropene.



Scheme 10. Synthesis of a bifunctional homotropilidene.



Scheme 11. Bi-1,2,4-triazines as bifunctional electron-poor dienes.



Scheme 12. Reaction products obtainable by (4+2)-cycloaddition of 3,6-bistetrazolo-1,2,4,5-tetrazine and subsequent reaction with acylating reagents.

Let us now change from synthetic aspects to the questions:

1. How do substituents in the diene and dienophile influence the reaction rate?

2. Can the "rules" derived from kinetic studies in one system be transferred to other systems, in this way predicting the reaction rate?

Two effects must be discussed in this connection, the electronic and the steric substituent effect. Any exchange of a small hydrogen against a larger substituent, either donor or acceptor, will reduce the rate of cycloaddition reactions. Let us first look at rate data for cycloaddition reactions of cyclic alkenes and substituted ones with 1,2,4,5-tetrazine, the parent compound. Two effects can be stated immediately (Table 1, Fig. 1).

1. The rate constants strongly depend on the ring size. Decreasing ring strain parallels decreasing rate constants with the minimum at the cyclohexene (derivative). This is a general phenomenon, as Fig. 1 proves for a number of analogous cycloaddition reactions [17, 18].

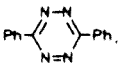
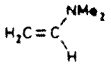
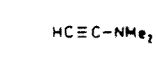
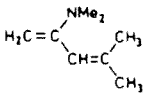
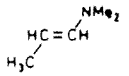
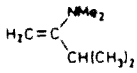
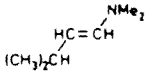
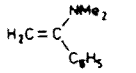
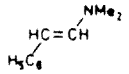
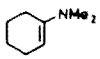
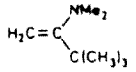
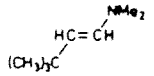
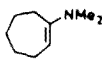
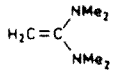
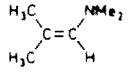
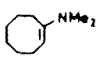
2. Donor substituents lift the HOMO of the dienophile and should increase the rate. This is only found as a clear-cut case for the highly reactive enamines. For the case of the enolethers and trimethylsiloxy alkenes, the hindering steric effect mentioned more than cancels the weak favoring electronic donor effect of the oxygen substituents.

An interesting interplay of steric and electronic effects is found in the reaction of α- and β-substituted enamines with 3,5-diphenyl-1,2,4,5-tetrazine (Table 2) [19, 20]. Without going into details for the explanation, let me state that the a-effect is mainly due to the hindrance of conjugation of the lone pair at the nitrogen with the alkene π-bond. With increasing size of the α-substituent, the lone pair at the nitrogen is twisted out of conjugation; in addition, a small hydrogen is exchanged against a larger substituent. Introducing the same substituents in a β-arrangement likewise reduces the rate; as long as the β-substituent holds the *trans*-position the retarding effect is a pure steric one, now we are also blocking the second carbon at the dienophile π-system. ^{13}C-measurements are in full accord with this explanation, as the chemical shift of the β-carbons show.

If these phenomena, ring size effect, angle strain, steric effect, and donor effect of substituents influence the rate of a reaction with a series of dienophiles in the same way for different heterocycles, then log k values for different systems should correlate in a linear way.

Figure 2 shows such a plot for the reaction of tetrazine dicarboxylate and the parent compound with a large number of dienophiles of different structure and size — and as one can see, the correlation is quite poor [17, 18]. Different steric effects are already filtered out, when we only separate the dienophile crowd into open-chain and cyclic dienophiles (Figs. 3, 4). This

TABLE 2. Rate Data for (4+2)-Cycloaddition Reactions of Enamines with 3,6-Diphenyl-1,2,4,5-tetrazine

Reaction with  , $10^7 \cdot k_2$ [l/mol · s], 20°C, dioxane					
	1 190 000		71 900		
	109 000		436 000		135 000 000
	28 700		4 460		4 490 000
	47		373		1 380
	1.2		2.9		255 000
	95		6.5		135

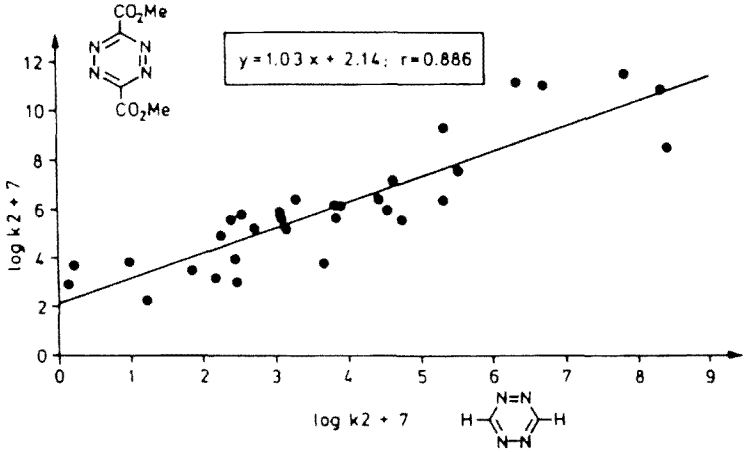


Fig. 2. Plot of log k values for the reaction of the same dienophiles with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate versus 1,2,4,5-tetrazine (dioxane, 20°C).

tells us that, keeping the steric requirement almost constant, electronic effects influence according to the FMO-theory and dictate the reaction rate in the same way, yet with different sensitivity. As one can see from the slope in both plots it is not one, but in favor of the more reactive tetrazine.

Substituents in the heterocycle should change the reaction rate in a predictable way. This is best demonstrated by keeping the dienophile constant and changing the tetrazine substituents. As predicted by the $LUMO_{diene} - HOMO_{phil}$ interaction, we found the same substituent dependence in principle using cyclooctyne, an enamine, or an ynamine (Table 3) as the dienophile [17-22]. Donor substituents in the tetrazine retard the reaction, acceptors increase the rate by many powers of ten. Again, when the steric effects are the same the log k values, using cyclooctyne or an enamine (Fig. 5), in both systems correlate showing the enamine to be the more selective dienophile. Finally, a comparison of the reactivity for an enamine and the ynamine for a number of differently substituted tetrazines shows a good linear correlation of the log k-values, too (Fig. 6), and almost the same selectivity with a slope close to one [19, 20].

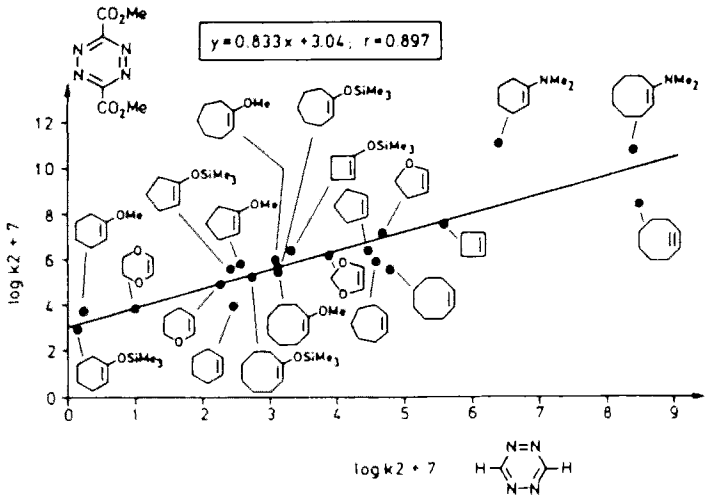


Fig. 3. Plot of log k values for the reaction of cyclic dienophiles with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate versus 1,2,4,5-tetrazine (dioxane, 20°C).

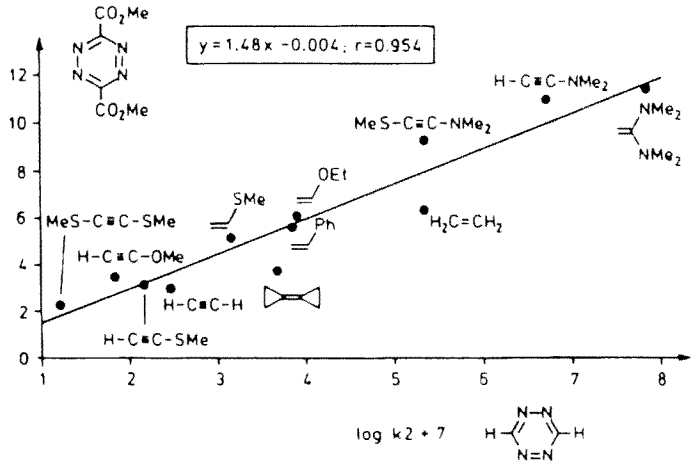


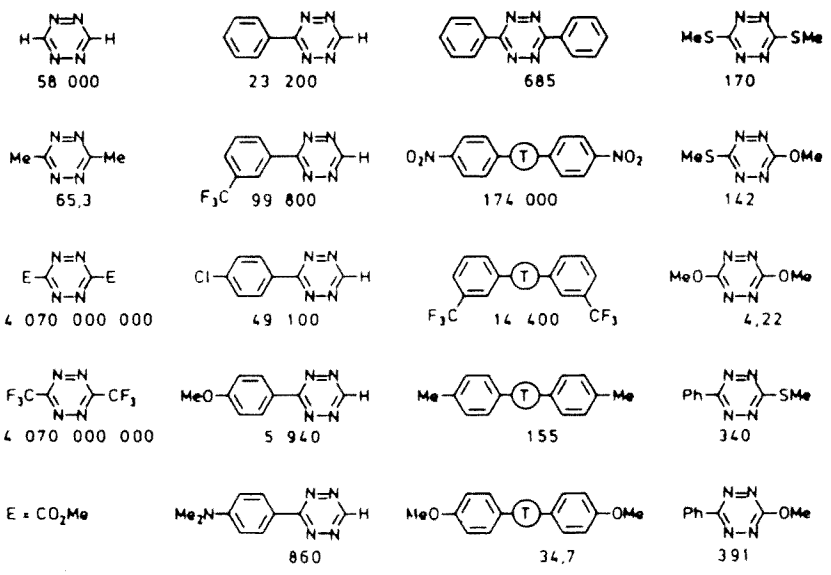
Fig. 4. Plot of log k values for the reaction of open chain dienophiles with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate versus 1,2,4,5-tetrazine (dioxane, 20°C).

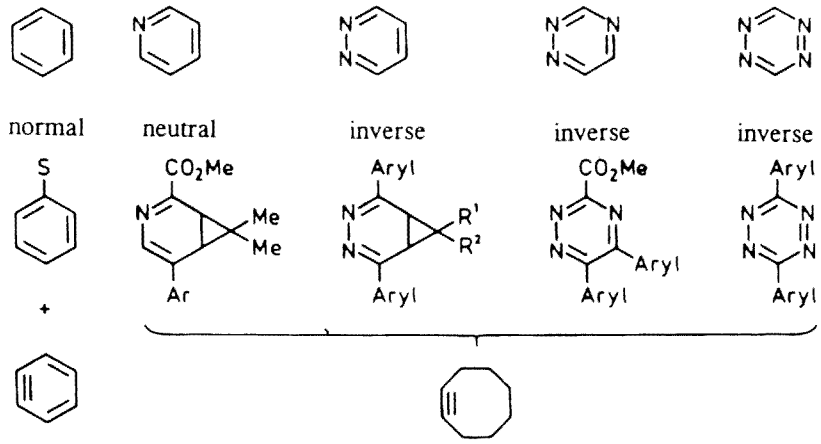
One might wonder why we used tetrazines with a great variety of five- and six-membered heterocyclic ring systems. This is demonstrated for an ynamine as the dienophile and five-membered heterocycles as substituents in the tetrazine (Table 4). Compared to phenyl as the reference substituent we find electron-donating and -accepting heterocycles as substituents. We presently are busy building up a series of σ-values according to Hammett's ideas for heterocyclic systems as substituents. This might be helpful to predict reaction rates in the field of heterocyclic chemistry [15-18, 23-26].

Under the influence of an increasing number of nitrogen atoms starting with benzene and finally arriving at tetrazines passing monoaza, diaza, and triazabenzenes, we come from normal Diels–Alder reactions to those with inverse electron demand. Where is the breakpoint of the neutral Diels–Alder reactions? We selected cyclooctyne and benzyne as rather comparable dienophiles and changed the number of nitrogen atoms: 1,2,4,5-tetrazine, 1,2,4-triazine, diazanorcaradiene, and monoazanorcaradiene as homoaromatic pendants. As one can see from the Hammett plots for substituted cases, the inverse type is obeyed for monoazanorcaradienes (Scheme 13) [27, 28].

TABLE 3. Rate Data for (4+2)-Cycloaddition Reactions of An Ynamine with 1,2,4,5-Tetrazines

Reaction with $Me-C\equiv C-NMe_2$, 20°C, $C_6H_5NO_2$, $10^4 \cdot k_2$ [l/mol·s]





Scheme 13. Influence of the number of nitrogen atoms in cyclic dienes on the electronic character of (4+2)-cycloaddition-reactions: From normal via neutral to inverse Diels–Alder-reactions.

Our interest in (4+2)-cycloadditions of thiones (thioketones) was raised by a telephone call from Rolf Huisgen asking for kinetic data in this field for comparison with similar data in the field of 1,3-dipolar cycloaddition reaction where thioketones had been approved as super dipolarophiles. When I told Rolf Huisgen that thioketones according to preparative working conditions should be lousy, unreactive dienophiles, he opposed, telling me that this is probably a prejudice. Try it experimentally was his advice, and we did [29].

Thiobenzophenones and thiofluorenones, nicely colored dienophiles, made it easy to follow preparative and kinetic runs. First we used alkyl and aryl substituted 1,3-butadienes because we had kinetic data for comparison with maleic anhydride and TCNE as dienophiles [30, 31].

The preparative yield is usually quite high, mostly close to quantitative for the raw product. Sometimes the purification made difficulties. Unsymmetrically substituted dienes react sometimes in a highly regioselective way, as shown by ^1H and ^{13}C

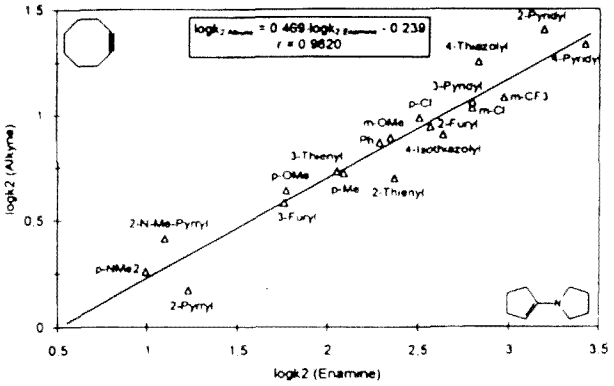


Fig. 5. Plot of log k values for the (4+2)-cycloaddition of cyclooctyne versus an enamine to 1,2,4,5-tetrazines.

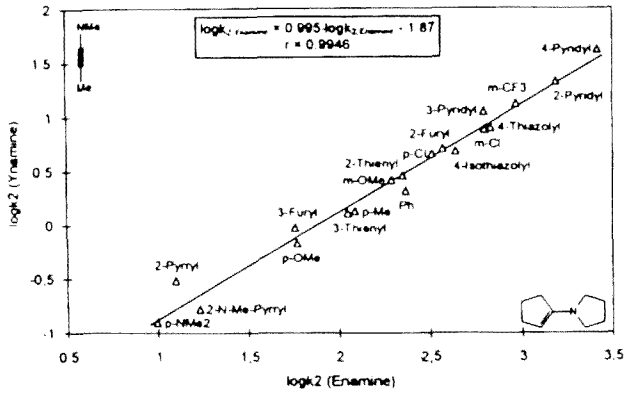


Fig. 6. Plot of log k values for the (4+2)-cycloaddition of an ynamine versus an enamine to 1,2,4,5-tetrazines.

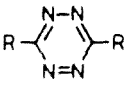
NMR studies. In two cases we found additional structure proof for the adducts by x-ray analysis for a 1-phenyl- and a 2-phenyl-substituted butadiene adduct [32, 33].

What are the results from the kinetic studies? Table 5 shows a comparison of thiobenzophenone with maleic anhydride as dienophiles for 1,3-butadiene and its derivatives. The k values clearly show that both reactions are normal Diels–Alder reactions, thiobenzophenone reacting in a $HOMO_{diene}-LUMO_{phil}$-controlled reaction, coming close to maleic anhydride in reactivity.

A comparison of thiofluorenone and thiobenzophenone shows an appreciably higher reactivity for the former thione, almost approaching TCNE in reactivity. So in fact thioketones are not only superdipolarophiles but also superdienophiles [29].

With a superficial look at the kinetic data shown, I explained these in terms of $HOMO_{diene}-LUMO_{phil}$-control. Introducing donor and acceptor substituents into the phenyl ring systems of 1-phenyl- and 2-phenyl-1,3-butadiene or the thione, we have a very sensitive probe to distinguish between normal, neutral, and inverse type Diels–Alder reactions of thioketones more precisely [29, 32, 33]. It turned out that thiones are just hikers between these three possible cases; seemingly simple changes in the components are responsible for the change. So the combination of substituted thiobenzophenones with 2,3-dimethylbutadiene belongs to the type of normal (4+2)-cycloadditions (Fig. 7), the combination of the same dienophile with substituted 1-phenylbutadienes follow the neutral case (Fig. 8). Finally, with the extremely electron-poor bistrifluoromethyl tetrazine as diene, the substituted thiobenzophenones behave as the donor component (Fig. 9); we have closed the circle now and come back to the 1,2,4,5-tetrazine system where we started.

TABLE 4. Rate Data for (4+2)-Cycloaddition Reactions of An Ynamine with Disubstituted 1,2,4,5-Tetrazines

Reaction of  with Me-C≡C-NMe_2, 20°C, CH_3CN, 10^4k_2 [l/mol·s]

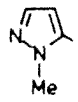
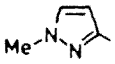
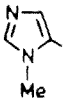
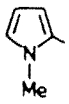
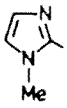
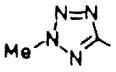
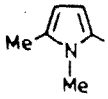
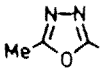
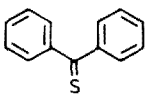
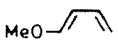
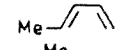
R = C_6H_5	1 820				
	1 150		10 050		2 560 000
	525		1 100		16 600
	426		319		4 660 000
	11.2		9 770		15 600 000
	3.69		10 200		293 000 000

TABLE 5. Rate Data for (4+2)-Cycloaddition Reactions: Comparison of Thiobenzophenone and Maleic Anhydride as Dienophiles

20°C, CH_2Cl_2, $10^6 \cdot k_2$ [l/mol·s] 30°C, dioxane

	diene	
718		92 040
129		841
109		
68.3		336
78.5		227
50.8		154
33.2		67.9

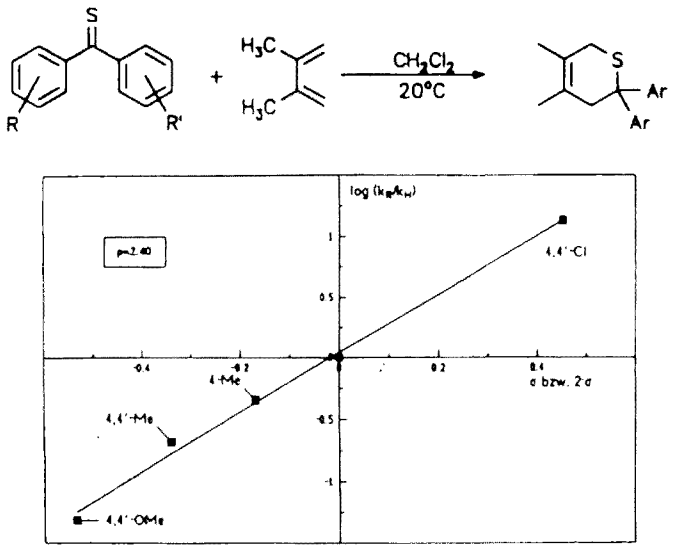


Fig. 7. Hammett-plot for the addition of substituted thiobenzophenones to 2,3-dimethylbutadiene.

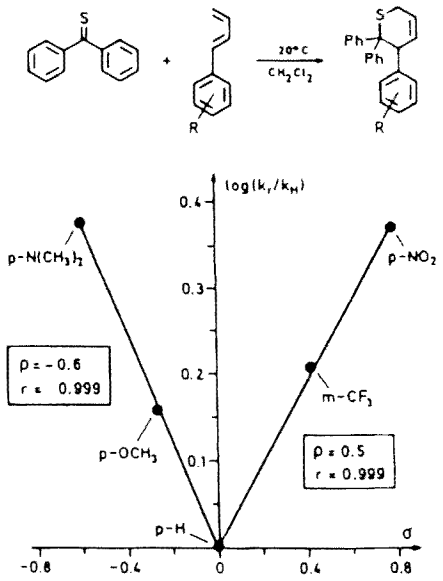


Fig. 8. Hammett-plot for the addition of thiobenzophenone to substituted 1-phenylbutadienes.

Time is too short to paint a complete picture with all the kinetic data available in our group. I think these data prove that we have valuable rules for the structure−reactivity problem in hand and are able to predict the reactivity of dienophiles and dienes in a reasonable way. Let me close this lecture by mentioning that we also have a wealth of data on the stereochemistry and regioselectivity of these cycloadditions, as well as on the solvent influence on rate. All of these data as well as the activation entropies tell us that the reactions under discussion are concerted, symmetry-allowed (4+2)-cycloaddition reactions.

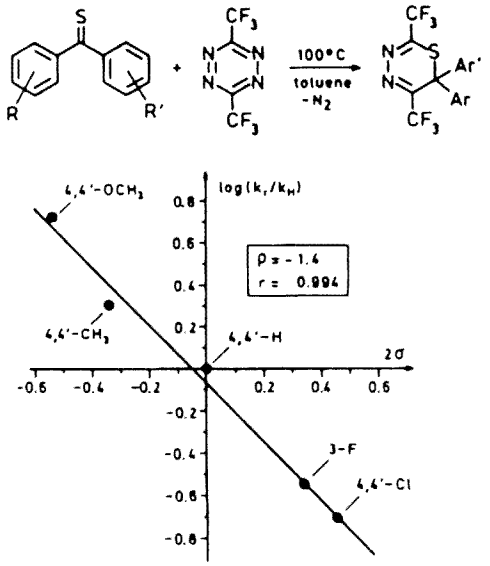


Fig. 9. Hammett-plot for the addition of substituted benzophenones to 3,6-bis[trifluoromethyl]-1,2,4,5-tetrazine.

In my opinion, the field of Diels–Alder reaction with inverse electron demand, actually the second half of this reaction type with regard to synthetic application, has developed in a very fruitful way within the last three decades. Boger, Seitz, Taylor, and van der Plas, just to mention a few names, have contributed quite a bit in this field. I have the feeling that we were not lazy, too, and that our kinetic contributions help to understand this important field in a more quantitative sense.

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