# *Rolf Huisgen:* Some Highlights of His Contributions to Organic Chemistry

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

***Rolf Huisgen*, Some Roots of His Success.** – *Rolf Huisgen* was a student of *Heinrich Wieland*, one of the most prominent Organic Chemists of the first half of the 20th century. The *Wieland* school was famous in natural products chemistry, isolation and determination of the constitution of, *e.g.*, steroids and alkaloids, and in synthesis. *Rolf Huisgen*, one of *Wieland*'s last students, worked on *Strychnos* alkaloids for his Ph.D.

The methodology of the time was still very classical: crystallization, distillation, and chemical-degradation procedures were the meager tools leading to success. *Wieland* did not only think in structures and synthesis, but also in reactivity. In a series of papers '*On the Occurrence of Free Radicals in Chemical Reactions*', he established himself as one of the fathers of *Free-Radical Chemistry* [1]. Through his famous series of publications on *Biological Oxidations* [2], he became one of the founders of modern dynamic biochemistry, and, likewise, a precursor of modern mechanistic thinking in Organic Chemistry. The *Wieland* school, therefore, definitely was one of the important roots for *Rolf Huisgen*'s success on his way to mechanistic thinking, and he has expressed this with high esteem for his academic teacher on many occasions.

His prime interest in dynamics and reactivity as a key to a better understanding of Organic Chemistry can be recognized already in his first independent research on the angular *vs.* linear fusion of aromatic rings starting from $\beta$-substituted naphthalenes and quinolines [3]. Although basic mechanistic investigations of *Hans Meerwein* and others, as well as the initiation of MO theory by *Erich Hückel*, had set the path for modern Organic Chemistry in Germany before, and despite the comprehensive publication of the '*Grundlagen der theoretischen Organischen Chemie*' by *Walter Hückel*, modern mechanistic approaches had its breakthrough in Germany mainly due to *Huisgen*'s work, which, of course, was stimulated by the British and American systematic Physical Organic Chemistry approaches of *Louis Hammett*, *Christopher Ingold*, *Paul Bartlett*, *Saul Winstein*, and others.

The application of kinetics became a magic wand in *Huisgen*'s hands, and his review in *Houben-Weyl* [4] on kinetic methods became a 'bible' for his students. Investigation of reaction mechanisms was for him, however, at no time an end in itself, but rather a tool to understand reactivity better for improving and expanding synthesis. By this typical '*Huisgen* approach', he gained understanding of reactivities in larger areas of Organic Chemistry than, probably, any other researcher. He never followed fashion trends in chemistry, but he rather set new trends himself, *e.g.*, in nitrogen chemistry, or

in cycloadditions and valence isomerization processes. *Huisgen*'s typical approach, which was another important root of his success, inspired a whole generation of younger chemists in Germany and not only in *Organic* Chemistry! This was due to his excellent lectures, his clear writing in publications, and his superb teaching.

None of his lectures about special fields of Organic Chemistry was ever repeated. The students were always guided to the frontiers of chemistry in an attractive modern field from the recent literature. He diligently and passionately introduced his research students to research, visiting them frequently, sometimes even daily at the bench, planning the experiments with them and introducing them to special techniques, like distilling mg quantities in a '*Huisgen* retort'. Later, he left them as much freedom as they could successfully endure, and opened their way to independent research. In the weekly group seminars, research problems, new developments, methodologies, and recent publications were discussed. A prominent seminar was, *e.g.*, when he surprised his audience by the benzyne hypothesis!

In this way, he created an atmosphere of open discussion and cooperation in the institute which attracted excellent students from Germany and many post-docs and visiting scientists from abroad. Guests became involved immediately into lengthy discussions, and their knowledge was squeezed from their tongue! The *Munich* laboratory became an international Mecca of Organic Chemistry, in the tradition of the times of *von Baeyer*, *Willstätter*, and *Wieland*. This scientific atmosphere was certainly another root for *Huisgen*'s success, exposing his own work almost daily to members of the 'I' of the field.

When one thinks back to the days in 1952, when he took over the chair of his teacher at the age of 32, when the laboratories founded by *Liebig* and kept at highest standards by his successors were still completely destroyed from World War II, it is unbelievable that *Huisgen* succeeded in planning and carrying out the reconstruction of a modern laboratory besides all his other achievements. This was due to another root of his success: his good physical constitution and his strong personal determination.

An important source of his success was, of course, his outstanding personality, which can only be humbly touched in this context. Therefore, we quote *Seeman* [5] who had asked *Huisgen:* '*What do you feel are your most important qualities*?'. The answer, given in ancient Greek as inscribed on the *Apollo Temple* at Delphi: '*γνωτι σεαύτον*' (know thyself), is not only the most concise way of self-recognition but also shows the impact of classic education, the antique, philosophy, mathematics, and of art on his personality. Then, *Huisgen* analyzes his approach to scientific advancement in more detail:

- *Not to be content with analogy, but ask for reasons within the limited realm of cognition*.

He warns not only of rootless speculation, he also points out the importance to ask nature clear questions, if one wants to obtain clear answers!

- *An intellectual property in connecting seemingly unrelated phenomena that sometimes lead to new principles*,

which is the basic principle for discovering the new in science!

- *A moderately good memory, one of the prerequisites of survival in chemistry*,

which could be recognized brilliantly in discussions with him over and over.

- *A love of detail, as that is the touchstone for the usefulness of principles and ideas.*

This brings us back to the observation, that theory and mechanism are mainly tools for him on the way to develop *new* Chemistry!

These statements demonstrate another root of *Rolf Huisgen*'s success, his exceptional unpretentiousness, which is apparent in his style of living as well as in the way in which he meets students, co-workers, and friends. A good example for his objection to prejudices, and his addiction to objectivity and impartiality is found in an article '*Heinrich Wieland als Mensch und Lehrer*' [6] where he writes: '*With concise words I want to draw a picture of Heinrich Wieland as academic teacher and man. I will do my best not to let the love and devotion of the scholar have a dominating and subjective influence in this context*'.

A particular important root of *Rolf Huisgen*'s success is a personal one: his wife *Trudl* was, at all times, an optimal partner; first as a fellow Ph.D. candidate in *Wieland*'s group, then as family mother and wonderful host at many occasions, and finally as his intimate confidante in all occasions of life. Her support of *Rolf*, and her readiness to let him concentrate on science and invest as much as he did into his profession, cannot be overestimated! Her recent death in February 2005 ended an almost 60-years enduring companionship of high mutual esteem.

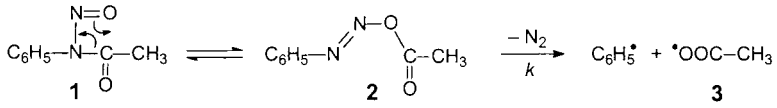
Many of these roots become apparent when one studies *Rolf Huisgen*'s research papers. Therefore, we have decided to present a few of his most typical and impressive studies demonstrating the broad scope of his research interests in different fields and times. They document the richness of *Huisgen*'s mind and the roots of his success, better than anything else.

**Nitroso Amides, Generators of Reactive Intermediates.** – The chemistry of nitrosoamides [7–9] and of the closely related diazo and diazonium compounds is like *Pandora*'s box in its multitude of reaction paths, leading to different types of reactive intermediates such as free radicals, carbenium ions, carbenes (*via* diazoalkanes), arynes, or, *e.g.*, azaquinodimethanes. *Rolf Huisgen* was one of the major players in this field for *ca.* 15 years, beginning 1945 in the early days of Physical Organic Chemistry. Few experimental or computational tools for exploring reaction mechanisms were available in those days. Even the application of kinetic methods in Organic Chemistry was rather new and spectacular.

The roots of *Huisgen*'s interest in this field are partly found in the research of *Heinrich Wieland*, his academic teacher, who had proposed in 1934 that phenyl radicals are responsible for phenylations of aromatic solvents by nitrosoacetanilide (NAA; **1**), benzenediazo hydroxide, dibenzoyl peroxide, or phenylazotriphenylmethane [10]. *Grieve* and *Hey* in England had come to the same conclusion at about the same time [11]. The observation, that *ortho*- and *para*-substitution were preferred for all types of substituents, when substituted benzenes were phenylated, discriminated these substitutions from the electrophilic or nucleophilic pattern. Quantum-mechanical calculations of *Wheland* have supported this interpretation [12].

Concentrating on NAA (**1**), it was a general belief in the fourties of last century that there exists a rapid equilibrium with benzene-diazoacetate (**2**) as first suggested by *Bamberger* [13]. According to *Hey* and *Waters*, the decomposition of the latter into phenyl, nitrogen, and acetoxyl radicals **3** was the first step of the phenylation reaction [14] (*Scheme 1*).

*Scheme 1*



*Huisgen*'s doubts about this interpretation were based on several arguments, the most stringent one being the absence of $CO_2$ among the products. The rapid decarboxylation of acyloxy radicals was known from the *Kolbe* electrolysis as well as from the thermal decomposition of diacetyl peroxide investigated by *Kharash* [13]. *Huisgen*'s approach for solving this and related questions concentrated on the following points:

*1*) A more-detailed kinetic investigation of the reaction system in order to clear the rate-determining step definitely.

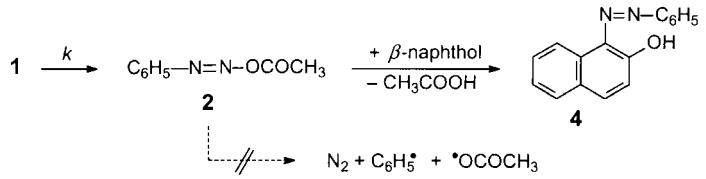
*2*) A more-detailed test for the postulated phenyl radicals as intermediates by competition experiments in phenylations of substituted benzenes.

*3*) How do the related aliphatic nitrosoacyl*alkyl*amines react?

*4*) What is the chemistry of aliphatic diazonium ions in nonpolar aromatic solvents?

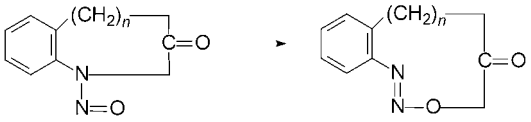
The thermal decomposition of **1** in dilute solution at 25°, as measured by $N_2$ evolution in a gas burette, followed first-order kinetics as previously observed by *Hey* [11]. The half-time varied by less than a factor of two in aromatic solvents but was much longer in AcOH and $CCl_4$ [7][8][15]. No $CO_2$ was formed. Very similar rates were observed when the kinetics were measured colorimetrically or by gravimetry. When $\beta$-naphthol was added to the solution of NAA (**1**), no $N_2$ was evolved but, instead, 1-phenylazo-$\beta$-naphthol (**4**) was formed (*Scheme 2*). Its concentration was measured by colorimetry or gravimetry. The rate constants were in qualitative agreement with those of $N_2$ evolution, but almost *no variation* with the change of solvent or the change of the coupling agent was observed. This result is the definite proof that the rate-determining step of the reaction is *not* the expulsion of $N_2$ as shown in *Scheme 1*, *but most likely the isomerization* **1** → **2**.

*Scheme 2*



This concerted isomerization mechanism required the (*E*)-configuration of the diazo ester **2** and *Huisgen*'s elegant experiments [7][15] on the rates of rearrangement of *N*-nitrosobenzolactams **5** to cyclic diazo esters **6** demonstrated convincingly that this was the case. Only when *n* was $\geq 3$ did the rearrangement occur, consistent with the (*E*)-configuration of the cyclic diazo ester product **6** (*Scheme 3*).

*Scheme 3*



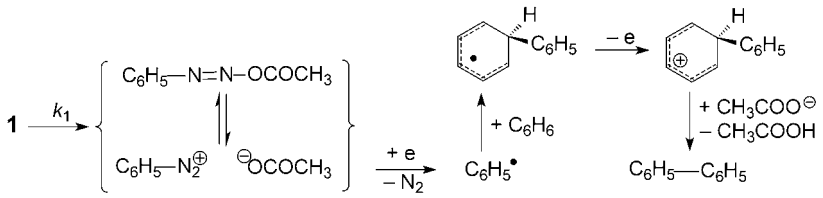

**5** **6**

It remained an open question why the rate constants of decomposition of **1** in aromatic solvents as measured by the $N_2$ evolution varied more than the colorimetric rates?

*Huisgen* concluded that the solvent must be participating in one way or the other in the $N_2$ expulsion and phenylation step. He discussed a crypto radical phenylation mechanism within a complex of the diazo ester **2** and the aromatic solvent, which even circumvented the formation of acetoxy radicals. If this was correct, then, however, the substitution pattern in the phenylation of substituted benzenes by NAA (**1**) *must differ from that for phenylazo(triphenyl)methane*, which was considered typical for the attack of free phenyl radicals. Since *ortho*, *meta*, and *para* rate constants cannot be measured directly and independently, *Huisgen* used – for the first time in his opus – the principle of competition [16] by which *relative* rate constants for the *o*-, *m*-, and *p*-positions are obtained from product analyses. Together with *Grashey*, he found the same relative rates for the substitution of a series of aromatic compounds, independent of the phenylation agent, phenylazo(triphenyl)methane or NAA (**1**) [16]. The phenyl radical intermediate was well-established this way.

By the research discussed so far, *Huisgen* has established the mechanism of the *first* and rate-determining step and of the *final* step of the phenylations by **1** (*Scheme 4*). The intermediate domain was still somewhat cloudy, in particular, since it was not clear at the time, whether the covalent diazoacetate *or* the related ionized diazonium acetate was the crucial intermediate for the coupling reaction, as well as the production of phenyl radicals, the former being generally the preferred species in nonpolar solvents [17]. It was shown later that, in $CCl_4$, the solvent in which NAA (**1**) released its $N_2$ much more slowly, crystalline diazonium carboxylates could be precipitated and analyzed [7][8][15][18], establishing their existence as intermediates in the NAA-decomposition mechanism. This conclusion, together with independent results for the related *Meerwein* phenylation in aqueous media [7][8][15][19], opened the door for an interpretation of the unresolved details of the mechanism of the phenylation reaction by NAA (**1**).

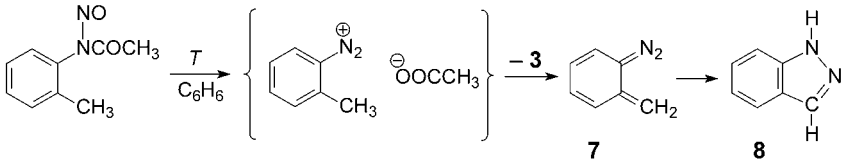
*Scheme 4*



It was proposed that the phenyl radicals are generated by electron transfer (or coupling and dissociation) to the diazonium ions by diazotate ions (or even NAA (**1**) itself) (*initiation)*, followed by a chain reaction, *e.g.*, like the one shown in *Scheme 4* [7][8][15][20]. The details must not be discussed here except for the fact that the aromatic solvent is taking part in the chain and, therefore, confirming *Huisgen*'s postulate of solvent participation in the phenylation steps! Besides, acyloxy radicals are no longer required, the carboxylic acid being formed from the carboxylate anion by protonation. Due to their high electron affinity, the diazonium ions are required as intermediates. When the reaction was performed in the cavity of an ESR spectrometer several nitroxide radicals, which could be formed by electron transfer, have been detected [8][15].

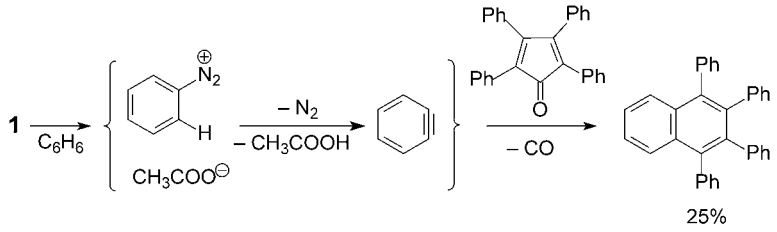
The high basicity of acetate in benzene solution [7][8][15][20] was now also made responsible for the formation of indazole **8** from *N*-nitrosoacet-*o*-toluidid *via* deprotonation of the *o*-toluenediazonium ion by acetate, generating the intermediate **7**, which then cyclizes to indazole [7][8][15][21] (*Scheme 5*). The deprotonation of the Me group is *faster* than the chain reaction leading to *o*-tolyl radicals!

*Scheme 5*




The carboxylate ion in nonpolar solvent proved even to be able to deprotonate benzenediazonium ions in decomposing solutions of *N*-nitrosoacylarylamines generating benzyne, which could be trapped by *Diels–Alder* reactions in good yield [7][8][15][22][23]. The benzyne generation also succeeded from the crystalline diazonium tetrafluoroborate by AcOK in benzene (*Scheme 6*) [22].

*Scheme 6*

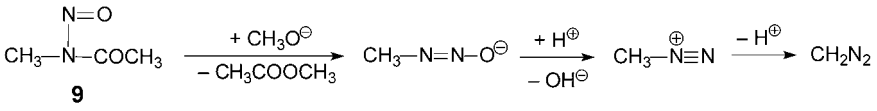



*Huisgen*'s initial kinetic experiments which had established the rate-determining step of the decomposition of NAA (**1**) and the formation of intermediate phenyl radicals have been the solid foundation, on which a wealth of Chemistry was developed subsequently.

*Huisgen*, in the mean time, had taken interest in the unexplored story of aliphatic *N*-nitrosoacylamides as, *e.g.* **9**, opening another pigeon-hole of the *Pandora*'s box of diazo chemistry! It was known from the work of *von Pechmann* and *Hantzsch* that aliphatic

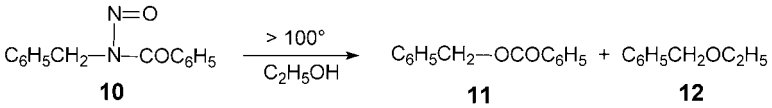
nitrosoamides were weak acylating agents, very similar to their aromatic counterparts [24]. By treating **9** with a strong base, such as KOH or methoxide, $CH_2N_2$ is formed *via* methyldiazotate and methyldiazonium ions and their deprotonation (*Scheme 7*).

*Scheme 7*



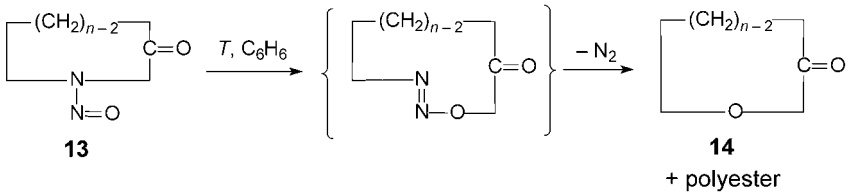

The thermal degradation of aliphatic nitrosoamides, however, required higher temperatures than the decomposition of the aromatic ones discussed above. As one of the early examples, *von Pechmann* had reported the formation of 25% benzyl benzoate (**11**) and 28% benzyl ethyl ether (**12**) from *N*-nitrosobenzoylbenzylamine (**10**) at 100° in EtOH, indicating clearly a *non*-radical pattern of decomposition [24] (*Scheme 8*).

*Scheme 8*




A kinetic investigation in *Huisgen*'s laboratory, following the $N_2$ evolution in aromatic solvents, gave excellent first-order rates, and displayed no typical solvent effect [25], but strong steric effects. The *rates* of isomerization of a series of cyclic nitroso lactams **13** were typically depending on the ring size, as shown previously in the aromatic nitroso lactam series. Low rates were found for $n = 5$ or 6, but 500000 times faster rates were observed for $n = 7-9$. When $n$ was increased further, rates similar to those for the open chain analogues were reported. Lactones **14** and polyesters were the main products (*Scheme 9*).

*Scheme 9*

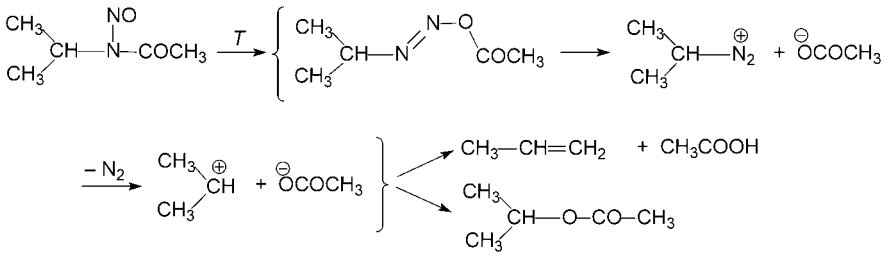



In addition, the rates of $N_2$ evolution of nitroso*alkyl*amides were increasing with the size of the alkyl *and/or* the acyl groups. These results were interpreted in detail by *Huisgen*, being best explained by the same 1,3-isomerization mechanism, which had been established in the aromatic series. This discussion, which includes strong arguments for the (*E*)-geometry of the intermediate diazo esters, will not be repeated here.

The difference between aromatic and aliphatic diazo esters (neither of which were, of course, ever isolated!) is their mode of decomposition after ionization to diazonium ions. Being not stabilized by conjugation, as aromatic diazonium ions are, the aliphatic

compounds split off $N_2$ in a fast follow-up step with formation of carbenium ions [26], as it was known for the deamination of aliphatic amines with $HNO_2$ or for the treatment of diazoalkanes with acids. In *non*polar solvents the typical products are esters and alkenes [26]. The *Scheme 10* probably is a somewhat simplified one, because, *e.g.*, *von Pechmann* had reported benzyl benzoate (**11**) as a main product, even when performing the decomposition of **10** in EtOH [24], the expected *solvolysis* product benzyl ethyl ether (**12**) being formed in almost equal yield; solvolysis products were also found in later studies in aqueous or alcoholic media [26]. As a consequence, *Huisgen*'s group investigated the fate of these carbenium ions in nonpolar solvents in more detail, and obtained deep insights into the chemistry of ion-pairs, which were discussed intensely by *Winstein*, *Cram*, and others at the same time for regular solvolysis reactions [27].

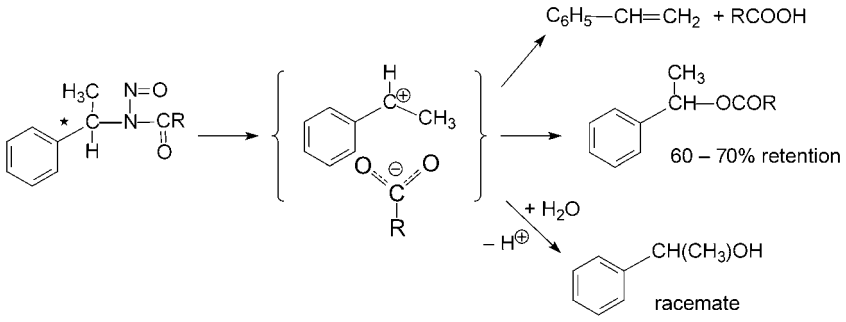
*Scheme 10*



The existence of *methyldiazonium benzoate ion-pairs* was supported by kinetic competition experiments, in which 4-nitrobenzoic acid was added to the decomposing solution of *N*-methyl-*N*-nitrosobenzamide in xylene: methyl benzoate *and* methyl *4*-nitrobenzoate were the products. By varying the ratios of the two acid components and, in addition, by decomposing *N*-methyl-4-nitro-*N*-nitrosobenzamide in the presence of benzoic acid, one and the same competition constant for the formation of the ester pair was found. In this way, complete exchange of the anion in the methyldiazonium carboxylate ion-pair was indicated. The same product ratio was found when $CH_2N_2$ reacted with a mixture of the two acids. The fast formation of H-bonds between the carboxylate ions, generated in the ion-pair, and the *added* carboxylic acid, probably plays an important role in this exchange process.

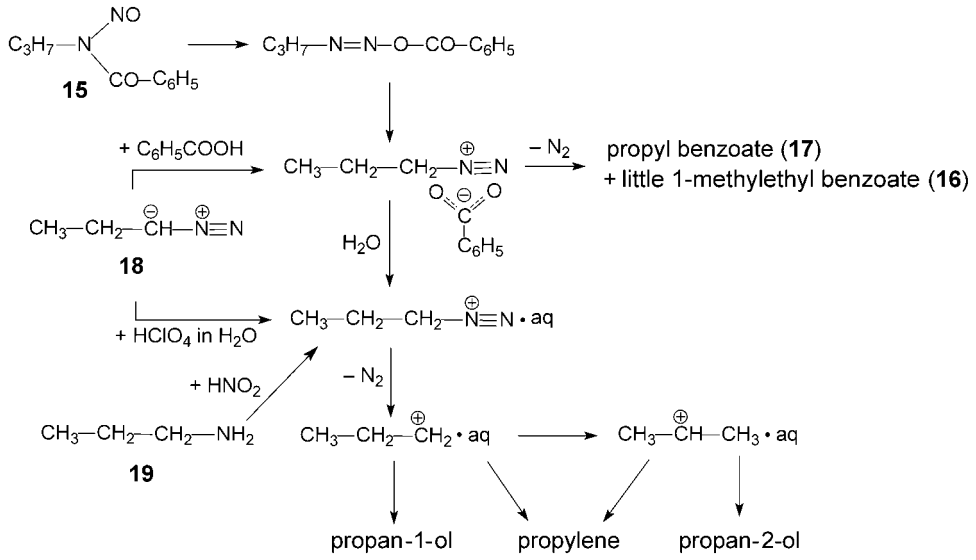
Deeper insight into the structure of the ion-pair intermediates of this reaction was obtained by an investigation of the stereochemistry of the reaction [28] (*Scheme 11*). In the thermolysis of optically active *N*-nitroso-*N*-(1-phenylethyl)acetamide (60°) *or* -benzamide (35°), 30–50% ester was formed besides styrene and acid. The esters were formed with 60–70% retention of configuration, depending on the acid component, the solvent, and possibly on the temperature. The higher the solvent polarity, the lower was the retention within the range given above, which supported the assumption of tighter ion-pairs in nonpolar solvents. In THF/$H_2O$ or in MeOH, the retention in the isolated 1-phenylethylcarboxylates was even higher, presumably because *external* ion-pair return is interrupted, and *internal* return is exclusively responsible for the ester formation. The solvolysis products, 1-phenylethanol or 1-phenylethyl methyl ether were mainly racemized.

*Scheme 11*



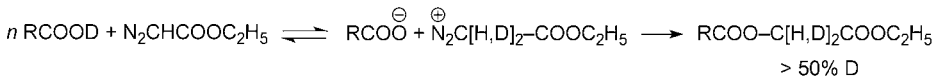

Further information on the structure and behavior of these types of ion-pairs was obtained when the phenomenon of carbenium ion rearrangements was investigated [29]. It was found, *e.g.*, that in the thermal decomposition of *N*-nitroso-1-propylbenzamide (**15**) in benzene only 1,5% of 1-methylethyl benzoate (**16**) was formed, besides the main product propyl benzoate **17** (*Scheme 12*). This is in excellent agreement with the reaction of 1-diazopropane **18** with benzoic acid in benzene. In the reaction of propylamine (**19**) with $HNO_2$ more than 30% propan-2-ol was analyzed in the alcohol fraction. Further, results of this detailed investigation supported the ion-pair hypothesis. The *internal* ion-pair return in nonpolar solvents is a fast process, and thus inhibits carbenium ion rearrangements in comparison to the longer life time of solvated carbenium ions in polar solvents. In *aqueous* solvents, the percentage of racemization is high, independent of whether the decomposition of *N*-nitrosopropylacetamide or the reaction of propylamine with $HNO_2$ is used.

*Scheme 12*



A final point to be investigated was the question of the equilibrium between alkyldiazonium ion-pairs and the corresponding diazoalkane and carboxylic acid. *Roberts* had shown, by using *O*-D-deuterated carboxylic acids, that the protonation of diphenyldiazomethane was irreversible, because only one D-atom was incorporated into the diphenylmethyl acetate. With diazoacetate (*Scheme 13*), on the other hand, incorporation of more than one D-atom into 1-(acyloxy)ethylacetate was found, establishing the reversibility of the protonation step [26][30]. By a similar method of D incorporation, *Huisgen* and *Stangl* showed that the maximal passage through the diazoalkane equilibrium amounted to 97% for Me, 72% for $PhCH_2$, 42% for i-Pr, and 39% for 1-phenylethyl when the corresponding *N*-nitroso*alkyl*amides were decomposed in nonpolar solvents. This result explains part of the racemization observed above for *N*-nitroso-1-phenylethylcarboxamides. In the ion-pair (*Scheme 11*), the product ester is actually formed with 85% retention. Although the nitrogen in diazonium ions is the best leaving group known, it is not safe to assume that its substitution follows always the $S_N1$ type mechanism.

*Scheme 13*



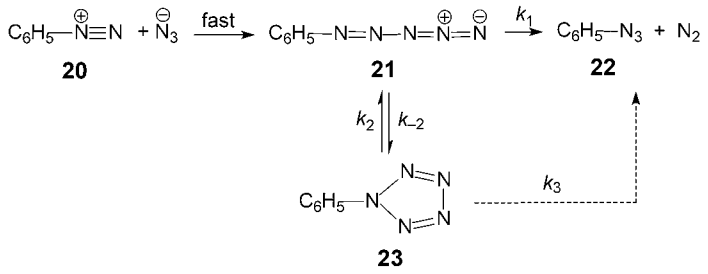

*Streitwieser*'s results for the deamination of optically active [1-$^2H_1$]butylamine in AcOH (69% ee (inversion)) suggest a $S_N2$ displacement of the diazonium N-atom at the primary C-atom and, consequently, in methyldiazonium ions [9]. Methyldiazonium fluorosulfonate, by the way, was shown to be stable at $-120°$ in $SO_2ClF$ [31].

*Huisgen*'s series of papers on '*Nitrosoacylamine und Diazoester*' in *Liebigs Ann. Chem.* were a kind of collecting first experiences in mechanistic research for his '*Adventure Playground of Mechanisms and Novel Reactions*' [15]. It was not the center of his research interests! It is impressive how the dynamic approach of kinetics and several other mechanistic tools succeeded in enlightening a jungle of reactions in diazo chemistry. Of course, competing research groups have also contributed, their merits are recorded in the references given below. Many of these results belong to the student's general knowledge today and are reported even in textbooks. In the fourties and fifties of the last century, however, they were at the frontiers of Organic Chemistry.

**Pentazole.** – The substitution of the N-atom in aromatic diazonium salts, formally by nucleophilic agents, was a standard synthetic procedure long before the fifties of last century, although the widely varying reaction conditions must have indicated differences in mechanism. While phenols are formed in boiling acidic solutions of diazonium salts, the introduction of chloride, bromide, cyanide, and some other reagents required $Cu^I$-catalysis at lower temperatures (*Sandmeyer* reaction). Without this catalysis, iodide or azide [32] are introduced at low temperatures. For the iodide reaction, the low redox potential of iodide was thought to be responsible, but the azide reaction remained a puzzle. *Hantzsch* had investigated this reaction, hoping to find a synthetic entrance to phenyl pentazole **23**, however, without success, phenyl azide being the sole product [33][34] (*Scheme 14*). A later study by *Clusius* and *Hürzeler* [33] with $^{15}N$-

labeled diazonium chloride added, at the time, more confusion than clarification to the understanding of this transformation, which occurred even at temperatures well below 0° (see below).

*Scheme 14*

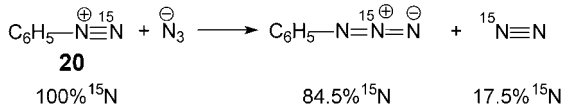



With this background, *Huisgen* and *Ugi* made an attempt to synthesize phenylpentazole by reacting the 'recently' published *covalent* aluminum azide [35] with 2,6-dibromo-*o*-quinone diazide in anhydrous THF [33], in analogy to the synthesis of phenyltetrazole from PhCN and the same azide [35]. Following *Huisgen*'s principle to collect as much information as possible from each experiment, the reaction vessel was connected to a gas burette. It was immediately realized that $N_2$ evolution started even at $-70°$, setting about half of the expected $N_2$ free on warming to $-20°$ (*primary nitrogen*). The evolution of the rest of the $N_2$ (*secondary nitrogen*) at $-20°$ followed first-order kinetics. 3,5-Dibromo-2-hydroxyphenylazide was isolated as product. *With this simple, well-designed quantitative experiment, the key to the solution of the* '*pentazole story*' [33] [34] *was immediately at hand*. It was quickly found [33] that also the reaction of benzenediazonium chloride in MeOH showed the same pattern, independent of the excess concentration of $LiN_3$: 98.5% $PhN_3$ and 100% $N_2$ were analyzed; at $-39.5°$, 76.5 mol-% of $N_2$ were formed by a first-order process with a half-life time of 4.6 min (*primary nitrogen*), the remaining 24% of $N_2$ were set free also in a first-order reaction at $-0.8°$ with a half-life time of 13.7 min (*secondary nitrogen*). It was concluded that the recombination of the phenyldiazonium (**20**) and $N_3^-$ ions was an immeasurable fast *primary* process, and the consecutive reactions of the intermediate phenyldiazoazide (**21**) were rate-determining. As independent evidence, it was shown that only seconds after mixing the coupling with $\beta$-naphthol failed.

This result was interpreted by a system of consecutive and parallel reactions as proposed in *Scheme 14*. It remained an open question whether the postulated intermediate phenylpentazole **23** decomposed *via* the diazoazide **21** ($-k_2$) or directly to phenylazide (**22**) by $N_2$ extrusion ($k_3$).

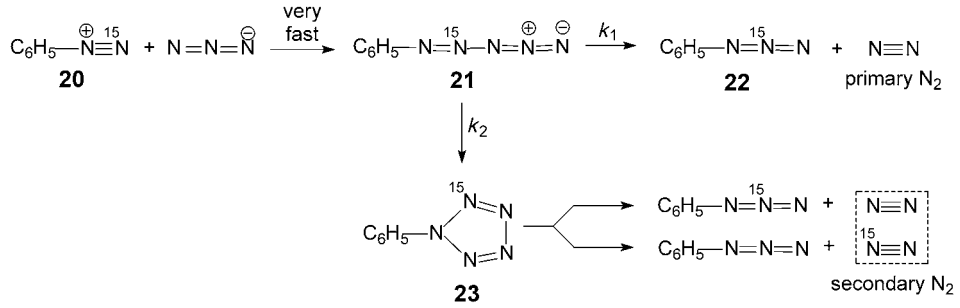
This proposal revealed, with respect to the $^{15}N$-labeling experiments of *Clusius* and *Hürzeler* mentioned above [33][34], that *a certain part of the $^{15}N$-label in diazonium salt* **20** *had turned up in the evolved $N_2$* (*Scheme 15*).

*Scheme 15*




It was shown that **20** formed 65% *primary* and 35 % *secondary nitrogen* in water as solvent. Because of the equivalence of the ring positions 2 and 5 in phenylpentazole (**23**), it was expected that 17.5% of the $^{15}$N-label in **20** (*Scheme 15*) turned up in the $N_2$ gas of the overall reaction, which was in excellent agreement with the results of *Clusius.* This interpretation was scrutinized in an *experimentum crucis* [33][34]: diazonium salt **20**, which was labeled in the terminal N-atom by $^{15}$N, was reacted with excess $LiN_3$ in methylglycole, and the *primary* and *secondary nitrogen* were collected separately at $-25°$ and at $0-10°$, respectively. It was found, by isotope analysis, that the *primary nitrogen* was free of $^{15}$N, as expected for its formation *via* **20** → **21** → **22** (*Scheme 16*); 25% of $^{15}$N was found in the *secondary nitrogen* in agreement with its formation via **20** → **21** → **23** → **22**.

*Scheme 16*




*By the combination of kinetics and $^{15}$N-labeling experiments, the constitution of phenylpentazole had been established before its isolation by crystallization* [36]! It was not possible, however, to answer conclusively, whether **23** decomposed *via* **21** or directly into phenyl azide (**22**) and $N_2$. The planar pentazole structure was established somewhat later by several crystal-structure analyses [37], and $^{15}$N-, $^{1}$H-, and $^{13}$C-NMR spectra were published [38].

The question of the ring closure of **21** → **23** was addressed by quantum-chemical calculations. *Huisgen* had assumed a bent structure for **21** instead of the linear arrangement shown in *Scheme 16*. Early calculations by *Roberts* by the simple *Hückel* LCAO method [39] had supported this and had shown that bending the N-chain in **21** is energetically not expensive, and that the bent structure of **21**, which is ideal for cyclization, is the most-stable one. Several more-sophisticated calculations have supported this result later and have shown that the pentazole ring structure is more stable than the diazoazide, due to its aromatic character [40].

The pentazole group at Ph is electron-attracting similar to the aldehyde or the $NO_2$ group. Accordingly, the thermal stability of arylpentazoles, as measured by kinetics

[33][38], is increased by electron-donating substituents and decreased by electron-attracting groups in the Ph ring. $\Delta H^{\neq}$ for the decomposition of the *p*-Cl-substituted **23** → **22** is 86.3 kJ mol$^{-1}$ and $\Delta S^{\neq}$ is 19.9 J mol$^{-1}$ K$^{-1}$ [38]. These data are believed to support the decomposition of **23** *via* **21** to **22**, as it was also suggested by *Huisgen* earlier, by analogy to the ring opening of tetrazoles [33].

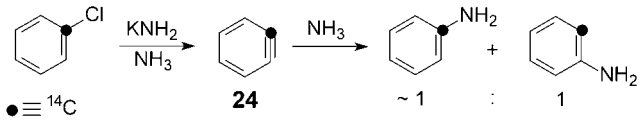
This *highlight* of *Huisgen*'s research shows admirably the strength of quantitative kinetic experiments for a better understanding of chemical reactivity. Kinetics was not an end in itself but it opened a rich and new field of chemistry. The discovery of pentazoles removed an outstanding blank area on the map of five-membered heteroaromatic rings! At the time of *Hantzsch* [33], methodology was not yet ripe for such an achievement.

**Benzyne – a Fascinating New Intermediate.** – Electrophilic aromatic and nucleophilic aliphatic substitution reactions are like fundamental pillars in the field of organic synthesis. In contrast, for many decades nucleophilic aromatic substitutions seemed to be by far less understood and of minor importance. Quite early, *Meisenheimer* explained reactions of so-called '*activated*' aromatic halides with nucleophiles by an addition–elimination sequence, and, in special cases, even stable '*Meisenheimer* adducts' could be isolated in pure form (for reviews, see [41][42]). But unexpected rearrangements in nucleophilic substitutions posed inexplicable problems in early times.

In a masterly review, *Bunnett* and *Zahler* collected these puzzling results, called '*cine substitutions*', re-opened the mechanistic discussion again, and stimulated new research in this area of nucleophilic aromatic substitution reactions (for a review, see [43]).

*Roberts et al*. could prove in 1953 in a brilliant tracer-study on the conversion of [1-$^{14}$C]chlorobenzene to [1-$^{14}$C] and [2-$^{14}$C]aniline by $KNH_2$ in liquid $NH_3$ a symmetrical intermediate, which they called benzyne (**24**) [44] (*Scheme 17*).

*Scheme 17*




This result suggested the analogous mechanistic pattern also for other nucleophilic substitutions at '*non-activated*' arylhalides, and the *Roberts* group could prove this assumption with the same experimental technique using labeled fluorobenzene + phenyllithium in ether [45] as well as labelled chlorobenzene + 4N NaOH at 350° [46].

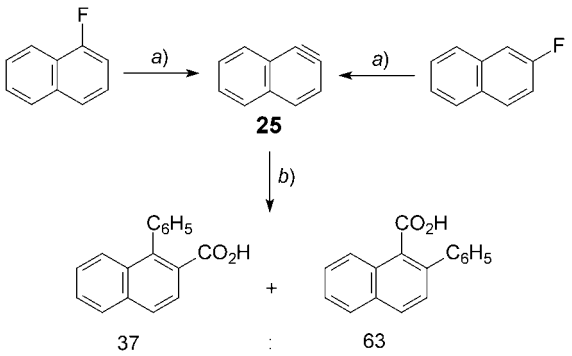
Possibly stimulated by *Bunnett*'s review and well-prepared by the fundamental studies of *Gilman* and *Morton* [47] and *Wittig* [48], the benzyne idea suddenly came to the fore within a very short time interval. *Huisgen* and his group was marching at the head of these fascinating discoveries for almost a decade (for a review, see [49]) [50][51].

*Huisgens*'s scientific tools, which helped him to elucidate many details of benzyne formation, benzyne structure, and benzyne reactivity were: extensive kinetic studies

and competition experiments to prove the intermediate formation of uncomplexed, '*naked*', benzyne in solution as well as the reactivity of this short-lived species. In many cases, *Huisgen* used what, at the time, were modern experimental techniques such as quantitative IR and UV spectroscopy, and quantitative vapor-phase chromatography.

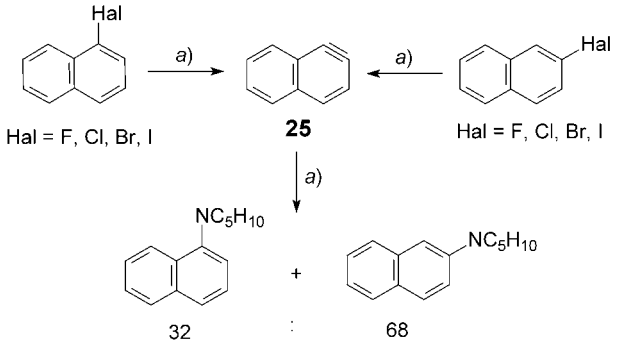
By using isomeric aromatic halides as starting compounds, *Huisgen* could establish the existence of the same intermediate for 'isomeric reaction paths' as *Schemes 18–20* demonstrate for selected systems.

*Scheme 18*




*a*) $C_6H_5Li$ in $Et_2O$, 35°. *b*) $C_6H_5Li$, then $CO_2$, then acidic workup.

*Scheme 19*

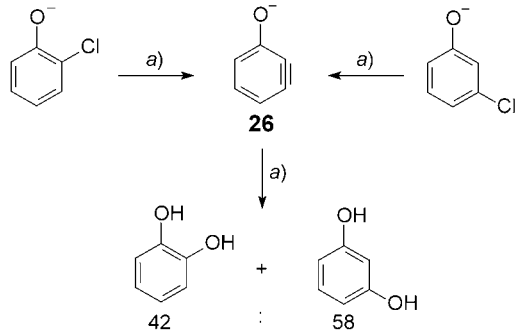



*a*) $LiNC_5H_{10} + HNC_5H_{10}$ in $Et_2O$, 20°.

With different nucleophiles (PhLi or lithiumpiperidide in $Et_2O$; molten NaOH) under quite different experimental conditions, dehydroaromatic systems naphth-1-yne (**25**) (*Schemes 18* and *19*) and benzyne-3-olate (**26**; *Scheme 20*) were intermediates in an elimination–addition sequence after an introductory metalation step.

Extensive kinetic studies in *Huisgens*'s group [52] finally revealed a more-detailed picture of the mechanism of aryne formation from aryl halides with lithium organic

*Scheme 20*



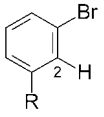

*a*) NaOH, 350°, then acidic workup.

compounds and lithium amides as strong bases and nucleophiles. *Tables 1* and *2* offer selected rate constants for the aryne formation with lithium piperidide in $Et_2O$.

Table 1. *Rate Constants of Benzyne Formation from Halobenzenes by Li Bases in $Et_2O$* (all rate constants ($10^5\ k_{exp}$) in $M^{-1}\ s^{-1}$)

| Li Base (equiv.) | $C_6H_5F$ | $C_6H_5Cl$ | $C_6H_5Br$ | $C_6H_5I$ |
|---|---|---|---|---|
| 2 $LiC_6H_5$ | 4.1 | 0.4 | 0.49 | 0.28 |
| 2 $LiNC_5H_{10}$ | 86 | 28 | 45 | 17 |
| 2 $LiNC_5H_{10}$ + 1 $HNC_5H_{10}$ | 48 | 26 | 73 | 28 |
| 2 $LiNC_5H_{10}$ + 2 $HNC_5H_{10}$ | 22 | 23 | 115 | 39 |
| 2 $LiNC_5H_{10}$ + 3 $HNC_5H_{10}$ | 16 | 22 | 150 | 52 |

Table 2. *Relative Partial Rate Factors ($k_p$) for the Metalation of H Vicinal to Br in* **27** (based on 0.5 for the H–C(2) of Bromobenzene (**27**; R = H)) *with Lithium Piperidide in $Et_2O$ at 20°*




**27**

| R | $k_p$ | R | $k_p$ |
|---|---|---|---|
| $CH_3$ | 0.35 | $CH_3O$ | 600 |
| $C_6H_5$ | 1.8 | Br | 940 |
| $(CH_3)_2N$ | 7.3 | F | 1700 |

The results of these and many more kinetic experiments may be condensed into a summary of some controlling factors and the mechanistic picture of benzyne formation as described in *Scheme 21*.

*1*) A reversible metalation step transforms the halide **28** to the *ortho*-metalated halobenzene **29**.

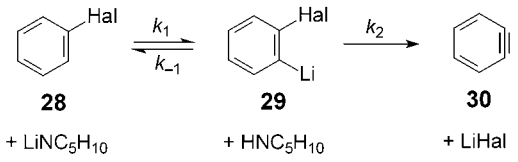
*2*) The rate of the metalation step is dictated by the inductive effect of *ortho*-subsituents.

*3*) Piperidine diminishes $k_{exp}$ by making the metalation step reversible. This factor loses weight as $k_2/k_{-1}$ increases from fluorobenzene to iodobenzene.

*4*) Further careful kinetic evaluations demonstrated $Et_2O$-soluble 1:1 complexes of LiHal with lithium piperidide being inactive in aryne formation.

*5*) Eliminated lithium halide finally complicates the kinetic scene still more because it is also able to add to benzyne as a nucleophile, as *Wittig* and *Hoffmann* could demonstrate in 1962 [53].

*Scheme 21*

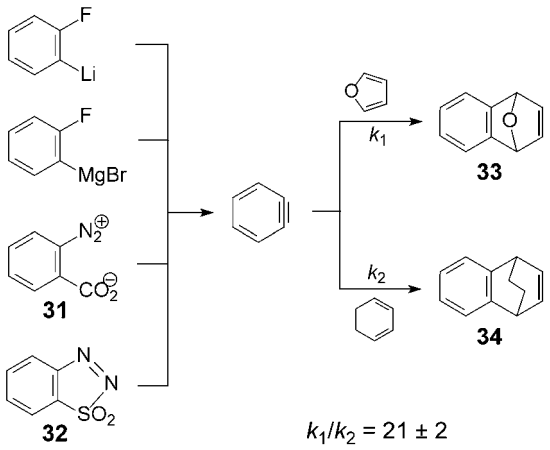



$$k_{exp} = \frac{k_1 \cdot k_2}{k_{-1}\,[HNC_5H_{10}] + k_2}$$

Already the data of *Scheme 19* demonstrate that the postulated intermediate, napth-1-yne (**25**) must be halogen-free, since the ratio of naphthyl piperidines $\alpha/\beta$ 32:68, is independent of the nature of the halogen in the starting 1- or 2-halonaphthalene. But as long as precursors are of metal-organic nature, complexes of the intermediate arynes with cations or metal halides cannot be ruled out definitely.

*Stile*'s reagent **31** and the benzyne precursor **32** are free from this suspicion. *Scheme 22* presents a brilliant competition system devised by *Huisgen* and *Knorr* [54].

*Scheme 22*




Furan and cyclohexa-1,3-diene were allowed to compete for benzyne of different provenance, the cycloadducts **33** and **34** were analyzed by GC. Identical competition constants $k_1/k_2 = 21 \pm 2$ establish the identity of the intermediate beyond doubt: benzyne must be '*naked*'.

Finally, competition constants in *Huisgen*'s hands were also suitable to offer information on the reactivity of arynes and nucleophiles as well. *Fig. 1* illustrates convincingly the influence of the aryne structure and substituents in arynes on the competition constant $\kappa$ for the addition of PhLi and lithium piperidide, showing the higher selectivity of arynes with extended $\pi$-systems toward PhLi in general. Donor substituents in arynes increase, acceptor substituents decrease the selectivity.

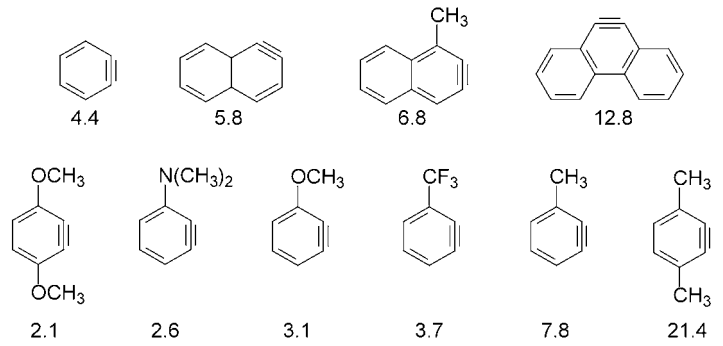



Fig. 1. *Competition constants* κ *of selected arynes for the addition of phenyllithium and lithium piperidide in* $Et_2O$

*Table 3* shows a scale of relative rates for different nucleophiles in the addition step to arynes. Lithium thiophenoxide outnumbers PhLi in spite of a basicity difference of nearly 30 p$K_a$ units; lithium thiophenoxide is not even basic enough to liberate phenanthr-9-yne from 9-chlorophenanthrene. Practically identical relative rate constants were measured for lithium piperidide and free piperidine ($k_{rel} = 100$); again the basicity difference of these nucleophiles amounts to *ca.* 25 p$K_a$ units.

Table 3. *Relative Nucleophilicity of RLi in the Addition to Phenanthr-9-yne in* $Et_2O$

| RLi | $k_{rel}$ | RLi | $k_{rel}$ |
|---|---|---|---|
| $C_6H_5SLi$ | 1700 | $(C_2H_5)_2NLi$ | 26 |
| $C_6H_5Li$ | 1300 | *t*-BuOLi | $< 3$ |
| $C_6H_5(CH_3)NLi$ | 38 | | |

Unsymmetrical benzynes offer an intramolecular competition system for the addition of nucleophiles, as demonstrated by the data in *Fig. 1*. *Huisgen* and *Herbig* studied a greater series of 3- and 4-substituted benzynes generated *in situ* from 2- and 4-substituted bromobenzenes; slow dropwise addition of PhLi to the aryl bromide in the presence of a large excess of piperidine in $Et_2O$ guaranteed that practically only free piperidine added to the aryne.

As the numbers in *Fig. 2* show, the inductive substituent effect is again working in the unsymmetrical addition step, stabilizing partial negative charges as formula **35** illustrates.

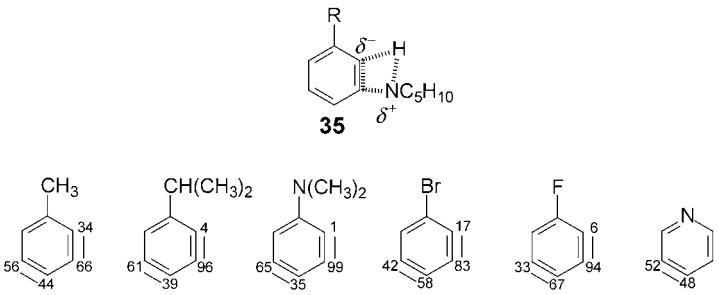



Fig. 2. *Regiochemistry of the addition of piperidine to 3- and 4-substituted benzynes* (the numbers indicate the product ratio with $NC_5H_{10}$ at the positions marked)

*Huisgen* left the field of benzyne chemistry early in the 1960s, his interest turned to electrocyclic reactions, and finally he developed the field of 1,3-dipolar cycloadditions.

In the meantime, benzyne chemistry has developed rapidly. Today, modern experimental techniques such as flash photolysis of different precursors in the gas phase, and IR, UV and MS investigations, as well as matrix isolation spectroscopy, allow deep insight into the structure of benzynes. Elaborate calculations confirmed early ideas about structure and bond lengths in benzyne and substituted benzynes [51].

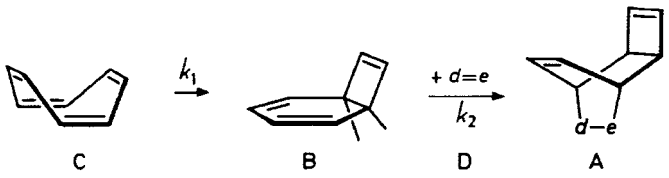
**Cyclooctatetraene (COT) – a Classical Problem of Organic Chemistry.** – When *Huisgen* occasionally was asked how to find a new attractive research field, he used to answer: '*Study the old literature and you will find enough problems – make them modern again*!' COT is such an 'old' molecule which, for many and completely different reasons, repeatedly attracted chemists' interest.

*Willstätter*, almost 100 years ago, was on the search for new aromatic systems. [55] He failed to synthesize cyclobutadiene, but, after a lengthy multistep synthesis starting with the alkaloid pseudopelletierine, he isolated a small amount of a yellow, unstable oil – cyclooctatetraene, as hydrogenation studies revealed [56]. Apparently, cyclic conjugation alone is not sufficient for aromaticity.

No detailed studies on COT were published for almost 40 years because of a lack of starting material, until finally *Reppe* opened the door to COT chemistry in 1948; the catalytic tetramerization of acetylene made ton quantities of COT easily available. The basic work on COT, which had been already conducted during World War II, was published in a comprehensive paper, the 'bible' of COT chemistry [57]. In *Reppe*'s hands, COT behaved like *Janus*-headed. While hydrogenation and epoxidation yielded products derived from the fourfold unsaturated eight-membered ring **C**, the reaction with dienophiles **D**, schematically d = e, produced a 1:1 adduct **A** derived from the bicyclic isomer **B** (*Scheme 23*).

In *Reppe*'s milestone paper, no decision could be made whether the skeletal rearrangement of COT to its bicyclic isomer **B** takes place before, during, or after the reaction with the dienophile d = e. It should be remembered, however, that no modern techniques were available at this time. $^1$H- or $^{13}$C-NMR spectroscopy and, even IR and UV spectroscopy were still far away from the experience of normal organic chemists.

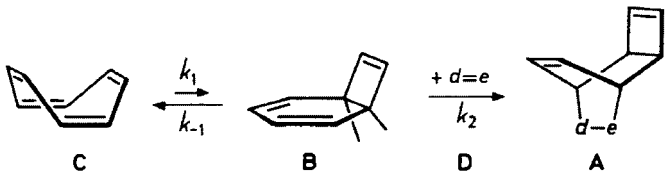
*Scheme 23*




This open mechanistic question soon attracted *Huisgen*'s interest [58]. In the late 1950's, he started extensive kinetic work in order to unveil the mystery of these COT reactions. He used the little known but very precise dilatometric technique, which actually should better be named '*contractometry*', because the combination of two molecules, *i.e.*, COT and the dienophile d = e, to give one, the *Diels–Alder* adduct, is accompanied by volume shrinking; this can conveniently and very precisely be observed by the sinking of the meniscus in the capillary of a cathetometer.

The kinetic illustration as sketched in *Scheme 24* can easily be treated by the steady-state treatment according to *Bodenstein* [59]: in a competing forward and reverse reaction, the concentration of the reversibly formed isomer **B** is based on $d[B]/dt = 0$, *i.e.*, the change of concentration of the bicyclic intermediate **B** can be neglected compared with the changes of **C** and **A**. In *Scheme 24*, the steady-state kinetics are developed.

*Scheme 24*




Steady-State Kinetics

$$d[B]/dt = 0 = k_1[C] - k_{-1}[B] - k_2[B][D]; \quad [B] = k_1[C]/(k_2[D] + k_{-1})$$

$$\frac{d[A]}{dt} = k_2[B][D] = k_1[C]\,\frac{k_2[D]}{k_{-1} + k_2[D]}; \quad k_d = k_1\,\frac{k_2[D]}{k_{-1} + k_2[D]}$$

The dilatometric rate constant, called $k_d$, depends on all rate constants in *Scheme 24*, *i.e.*, $k_1$, $k_{-1}$, and $k_2$. A large excess of dienophile **D** is used in the dilatometric procedure, always guaranteeing overall first-order kinetics.

*Fig. 3* illustrates how $k_d$ depends on the dienophile concentration **D**, for the limiting cases, case *1* and case *2*, and the intermediate range.

For limiting case *1:* $k_{-1} \gg k_2[D]$
For limiting case *2:* $k_{-1} \ll k_2[D]$
For intermediate range: $k_{-1} \approx k_2[D]$

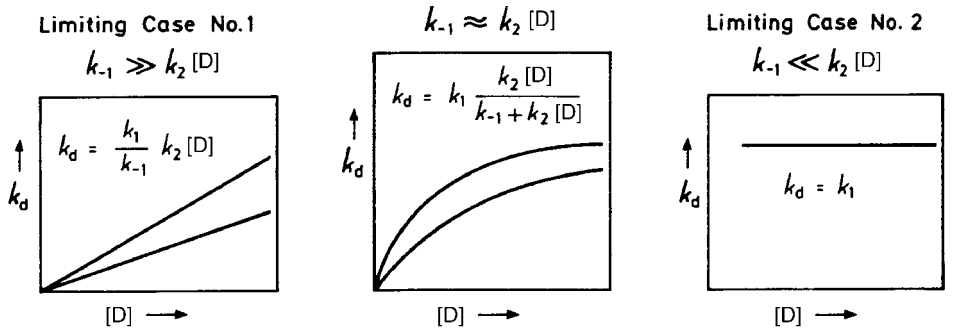



Fig. 3. *Graphical representation of the dependence of* $k_d$ *on [D] for the competition system of* Scheme 24

*Limiting case 1:* As long as $k_{-1}$ is large compared to $k_2$ [D], the latter factor can be neglected in the denominator of *Scheme 24*, and the expression for $k_d$ simplifies to $k_d = k_1/k_{-1} \cdot k_2$ [D]. The intermediate, bicycle **B,** is trapped from the equilibrium with **C** by d = e. This rate law is observed for less-reactive dienophiles, for instance, maleic anhydride [58].

*Intermediate range:* In this concentration range of dienophile, $k_2$ [D] competes with $k_{-1}$. When $k_d$ is plotted against [D], curves are expected which approach a plateau at higher dienophile concentration. The diagram in the middle of *Fig. 3* demonstrates this behavior.

*Limiting case 2:* When highly reactive dienophiles are used, $k_2$ [D] exceeds $k_{-1}$ in the denominator; the dilatometric rate constant $k_d$ then equals $k_1$, being independent of [D].

Tetracyanoethylene (TCNE) and dicyanomaleimide are record dienophiles [60]. Dilatometric rate measurements with COT using increasing dienophile concentrations furnished curves approaching a plateau as demonstrated in *Fig. 4*.

The equation on the left side of *Fig. 4* is easily transformed to a linear equation (right side of *Fig. 4*), when $k_d$ is plotted against $k_d$/[D]. The intercept at infinitely high concentration of **D** equals $k_1$, being independent of the dienophile within the error limit. The slope of the straight line is identical to $k_{-1}/k_2$, indicating that dicyanomaleimide is five-times more reactive than TCNE as dienophile.

These kinetic experiments prove that the *Diels–Alder* reaction must be preceded by a reversible first-order isomerization of COT; the most reasonable assumption is that bicyclo[4.2.0]octatriene **B** (*Schemes 23* and *24*) is this intermediate, formed from COT in a reversible electrocyclic reaction [61]. By the same technique, dilatometric measurements, *Huisgen* proved the analogous reaction sequences for [4+2] cycloadditions of phenylcyclooctatetraene with different dienophiles [34][58].

Temperature-dependent '*Bodenstein* plots', named in honor of *Max Bodenstein*, the pioneer of the steady-state principle in chemical kinetics, as shown in *Fig. 5*, allowed the calculation of activation parameters for $k_1$, the rate constant of the valence isomerization of COT $\rightleftharpoons$ bicyclo[4.2.0]octatriene (*Fig. 5*).

All of these experiments gave access to the values of $k_1$ and $k_{-1}/k_2$, but unfortunately not to the equilibrium constant $K = k_1/k_{-1}$ itself. To obtain at least an approximate value of *K*, *Huisgen* used, as he sometimes joked, a 'dirty trick', employing the rate constant

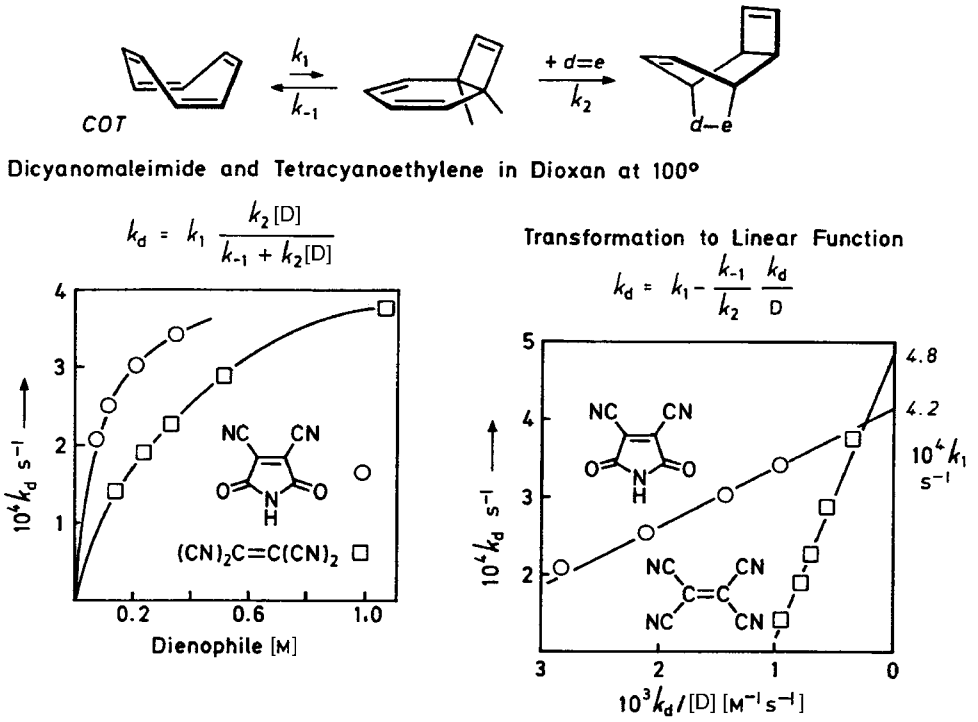



Fig. 4. Diels–Alder *reaction of tetracyanoethylene (TCNE) and dicyanomaleimide in dioxane at 100°*. Plot of $k_d$ *vs.* [D] (*left*) and $k_d$ *vs.* $k_d$/[D] (*right*)

$k_2$ for the [4 + 2] cycloaddition of the structurally related and stable bicyclo[4.2.0]octa-2,4-diene (see *Fig. 5*), with TCNE as a model [34]. In *Fig. 5*, the full energy diagram for the electrocyclic reaction of COT to bicyclo[4,2,0]octatriene is included – only 0.01% of the bicyclic isomer is present in equilibrium at 100° in dioxane.

How do these experimental results obtained in the early 60's by *Huisgen* compare with literature data? *Vogel et al.* [62] isolated bicyclo[4.2.0]octa-2,4,7-triene, obtained by debromination of COT-dibromide with Zn at −78°, as a stable compound, which rapidly reverted to COT at 0° by an electrocyclic ring opening. *Squillacote* and *Bergman* [63] established the electrocyclic equilibrium COT ⇌ bicyclo(4.2.0)octa-2,4,7-triene in the gas phase between 400–700° and at $10^{-5}$ Torr. $^1$H-NMR Analysis of the frozen samples allowed the measurement of the equilibrium mixtures, furnishing $\Delta G(100°) =$ 7 kcal mol$^{-1}$, in perfect agreement with *Huisgen*'s value obtained *via Diels–Alder* kinetics.

*Huisgen*'s 'kinetic key' to analyze complex kinetic systems was successfully applied by himself and others in a number of other systems, such as the conrotatory thermal ring opening of *trans*- and *cis*-1,2-diphenylbenzocyclobutene [34], the electrocyclic ring opening of aziridines to azomethine ylides, [34] the valence isomerization of *Vogel*'s bridged 10$\pi$-systems [64], or electrocyclic reactions such as cyclohepta-1,3,5-triene ⇌ bicyclo[4.1.0]hepta-2,4-diene [34] and its aza analogues 3-aza-hepta-1,3,5-triene ⇌ 3-

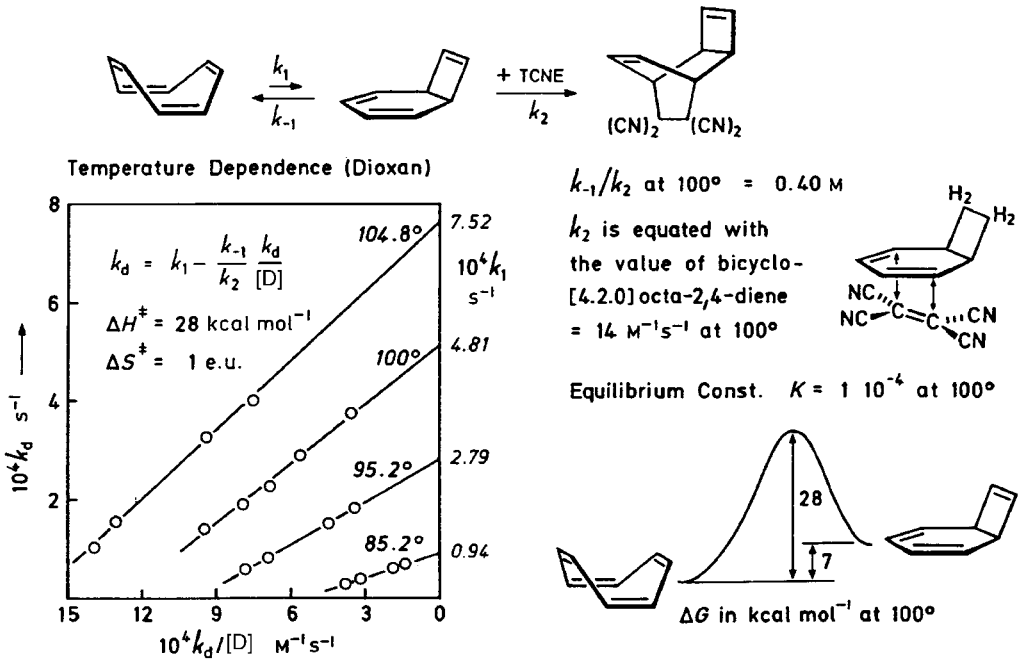



Fig. 5. Diels–Alder *reaction of cyclooctatetraene (COT) with TCNE at different temperatures and energy profile for the electrocyclic reaction COT ⇌ bicyclo(4.2.0)cycloocta-2,4,7-triene*

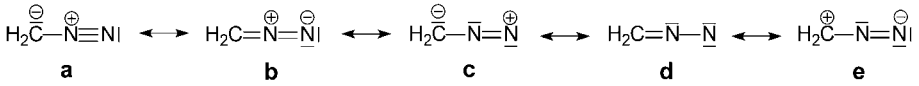
aza-bicyclo[4.1.0]hepta-2,4-diene [65]. So, *Huisgen*'s 'kinetic method' applied to the 'simple' COT case turned out to be of general applicability.

**1,3-Dipolar Cycloadditions.** – 1,3-Dipolar cycloadditions, the concept of which was conceived by *Rolf Huisgen* at the end of the 1950s, constitute his most extensive research efforts. Even today, he actively contributes to the development of experimental and theoretical aspects of these reactions. The aim of this part of the highlights of *Rolf Huisgen*'s contributions to organic chemistry cannot be a comprehensive survey on the achievements of the Munich laboratory in this area. More than 130 publications have appeared so far. This demonstrates the wealth of results, which have accumulated over the decades. A survey on 1,3-dipolar cycloadditions up to 1984 has been given by *Rolf Huisgen* [66] in a two-volume compendium on 1,3-dipolar cycloadditions edited by *Padwa* [67].

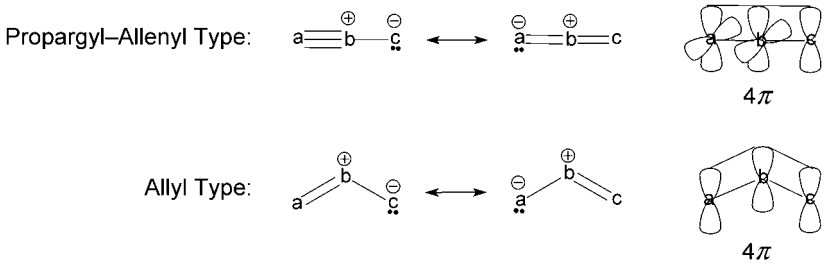
The origin of the concept of 1,3-dipolar cycloadditions may be traced back to a review article on the chemistry of diazoalkanes by *Rolf Huisgen* published in 1955 [68]. In this publication, resonance structures of $CH_2N_2$ can be found, which anticipate the valence-bond description of 1,3-dipoles (*Scheme 25*). *Rolf Huisgen*'s breakthrough consisted in the realization that this description of diazoalkanes can be extended to a series of similar structures, in which the elements, carbon, nitrogen, and oxygen are permuted [69][66]. Considering the valence nature of these elements, eighteen 1,3-dipoles of either propargylic-allenylic or of allyl type, can be generated (*Scheme 26*)

[66]. When elements of the second row of the Periodic Table, like sulfur and phosphorous are included, even more 1,3-dipoles can be envisaged. Not all of these 1,3-dipoles constituted new chemical entities. Some of them, including diazoalkanes and their cycloadditions, had been investigated earlier [68]. The development of the concept, however, is a demonstration of the power of simple qualitative valence-bond theory in describing chemical structures. Research in this new area immediately boomed in *Rolf Huisgen*'s group and led already in 1963 to two review articles [70][71]. The principle of 1,3-dipolar cycloadditions constitutes a powerful tool in the synthesis of five-membered heterocyclic rings, shown schematically in *Scheme 27*.

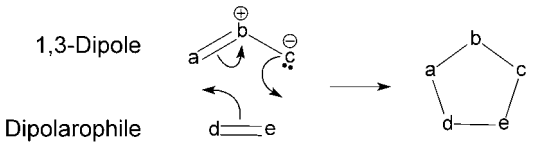
*Scheme 25*




*Scheme 26*



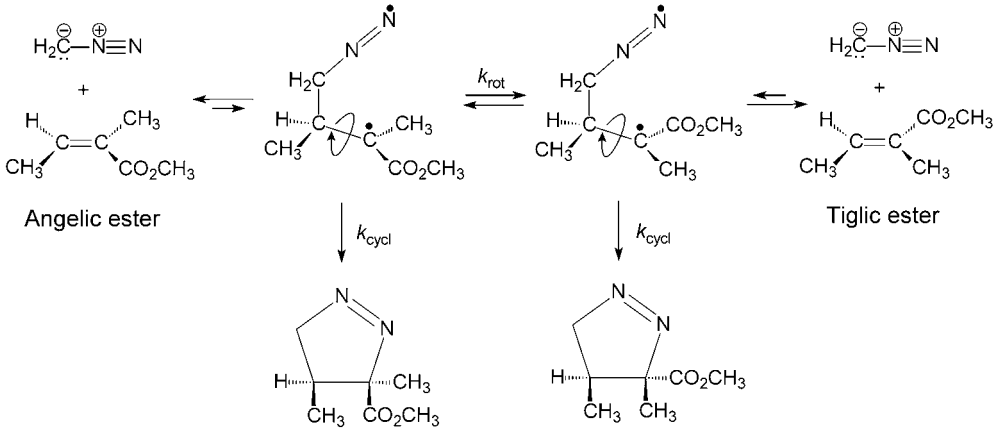

*Scheme 27*




*Rolf Huisgen*'s approach to Chemistry always includes mechanistic aspects. Thus, it was no surprise that, at the beginning, kinetic measurements of the rate of cycloaddition of diazoalkanes to a series of alkenes of systematically varying electron deficiency played a major role [72]. Soon, when the reactivity of other 1,3-dipoles towards similar series of alkenes was studied, it was realized that there exist similarities in the reactivity patterns, which, however, displayed also characteristic differences [66]. Solvent dependencies of the rates of cycloaddition, together with stereochemical studies on the retention of stereochemistry of the alkenes in the cycloadducts, provided evidence that the two new $\sigma$-bonds must be formed at the same time, leaving no possibility of stereochemical scrambling in the part of the alkene during the cycloaddition process [71].

The problem of concerted or consecutive formation of the two new $\sigma$-bonds, in particular *via* biradical intermediates, provoked a heavy dispute between *Firestone* [73] and *Huisgen* [74]. Many arguments were exchanged, which resulted in more and more sophisticated stereochemical studies. In 1978, the Munich group published on the stereospecificity of $CH_2N_2$ cycloadditions to the *cis*/*trans*-isomeric esters methyl angelate and methyl tiglate (*Scheme 28*) [75]. Chromatographic techniques were applied in order to push the experimental detection limit of the 'wrong' isomer as far as possible. It was demonstrated that the cycloaddition of methyl angelate to $CH_2N_2$ proceeds with a stereospecificity $>99.94\%$, and the cycloaddition of methyl tiglate to $CH_2N_2$ with a stereospecificity of $>99.997\%$. This certainly is a world record in precision. If biradicals, as shown in *Scheme 28*, had been involved, ratios of $k_{cycl}/k_{rot}$ of $>1700$ and 33000, respectively, would have been necessary to explain the experimental result. This, in turn, would have required unrealistically high rotational barriers in the biradical intermediates. Thus, the result strongly supported a concerted cycloaddition.

*Scheme 28*



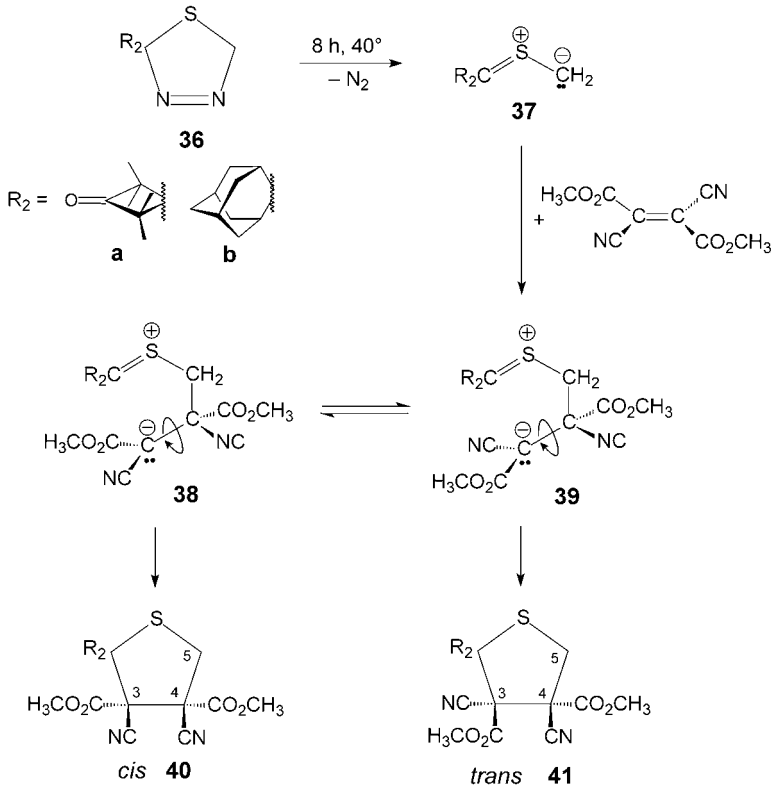

| | | |
|---|---|---|
| Analyt. Limit: | 0.06% | 0.0030% |
| Stereospecificity: | > 99.94% | > 99.997% |
| $k_{cycl}/k_{rot}$: | > 1700 | > 33000 |
| $\Delta\Delta G^{\ddagger}$ [kcal mol$^{-1}$]: | 4.4 | 6.2 |

At the time of the mechanistic investigations, the rules of conservation of orbital symmetry were published by *Woodward* and *Hoffmann* [61]. *Rolf Huisgen* realized immediately, when the first communications appeared in 1965 [76], the power of this tool for 1,3-dipolar cycloadditions [77]. The concerted nature of 1,3-dipolar cycloadditions seemed to be undisputable. Thus, *Rolf Huisgen* must have favored *Woodward*'s postulate: '*Exceptions, there are none*'. A further argument in favor of the concerted nature was seemingly provided by the interpretation of reactivity scales of 1,3-dipoles in terms of frontier molecular orbital theory, [78] an approach which originated in *Fukui*'s ideas [79].

The concerted nature of pericyclic reactions constituted an undisputed dogma in the early days after the publication of the *Woodward–Hoffmann* rules. Among these, 1,3-

dipolar cycloadditions were interpreted in terms of a concerted process. Soon, however, a search for the limits of the rules started. *Doering* and *Roth* defined the 'energy of concert' as a measure of preference for a pericyclic reaction [80]. It is characteristic of *Rolf Huisgen*'s approach to chemistry that he questions the belief in rigid rules. Reflections on the consequences of the FMO model for concerted or stepwise cycloadditions suggested to him that the cycloaddition of a thiocarbonyl *S*-methylide to very electron-deficient dipolarophiles might induce a two-step cycloaddition, presumably *via* a zwitterionic intermediate. It is of no surprise that he was the first to find experimental evidence of such a cycloaddition [81]. A bulky substituent at one side of the thiocarbonyl *S*-methylide was assumed to support the formation of an open intermediate, a zwitterion. The results of a study on the stereospecificity of the reactions of 2,2,4,4-tetramethylcyclobutan-1-one-3-thione *S*-methylide and adamantanethione *S*-methylide to dimethyl 2,3-dicyanofumarate are depicted in *Scheme 29*.

*Scheme 29*




Nitrogen evolution from the spiro-1,3,4-thiadiazolines **36a** and **36b** in THF furnished the two 1,3-dipoles **37a** and **37b**, respectively, which combined *in situ* with dimethyl 2,3-dicyanofumarate to give the *cis,trans*-isomeric cycloadducts **40** (**a** and **b**) and **41** (**a** and **b**) in 94% yield and in a ratio of 48:52 for **36a**, and in 90% in a ratio of 41:59 for **36b**. Dimethyl fumarate, however, afforded stereospecifically only one

cycloadduct in 99% yield, the corresponding reaction with dimethyl maleate furnished 82% of a mixture of the adducts of dimethyl maleate and dimethyl fumarate in a ratio of 98.9 : 1.1, which was interpreted in terms of a minor contribution of the two-step reaction to the otherwise concerted cycloaddition. *Scheme 29* shows the zwitterionic intermediates **38** and **39**. In the case of tetracyanoethylene, the zwitterionic intermediate could be intercepted [82]. Subsequently, the zwitterionic pathway could be substantiated further by the Munich group [83]. Other examples of two-step 1,3-dipolar cycloadditions have been found by *Quast et al.* [84], and *Sauer* and co-workers [85]. *Quast* isolated zwitterions in the reaction of strongly electrophilic azides with 5-alkylidenedihydrotetrazoles, which were presumably intermediates in the cycloaddition. *Sauer* and co-workers unveiled non-stereospecificity – evidence for a two-step zwitterionic cycloaddition – in the reaction of electrophilic azomethine ylides with enamines. In both of these examples, the electronic character of 1,3-dipole and dipolarophile is reversed as compared to the example given by *Huisgen*.

The realization that substituents in 1,3-dipole and dipolarophile will not only influence the rate of cycloaddition but also the mechanism convinced *Rolf Huisgen* that mechanisms of 1,3-dipolar cycloadditions might change, when specific conditions are met. In this connection, another feature of *Rolf Huisgen*'s character becomes apparent. New developments, here, in particular, the increase in importance of quantum-chemical calculations for mechanistic problems, were immediately recognized and incorporated in his investigations. Collaborative efforts started, which unveiled the 'superdipolarophilic' nature of the C=S bond in nitrone cycloadditions by *ab initio* calculataions [86]. Experimental studies had established the high reactivity of the C=S bond in these cycloadditions [87] and were also described for *Diels–Alder* cycloadditions by *Sauer* and co-workers [88].

Cycloadditions of thioketones to thiocarbonyl *S*-ylides were the '*adventure playground*' for further experimental and theoretical studies, which influenced the mechanistic representation of 1,3-dipolar cycloadditions. The observation that $N_2$ extrusion from 1,3,4-thiadiazolines, the primary products of the *Schönberg* reaction [89], provides a simple access to the otherwise unstable thiocarbonyl *S*-ylides has interested *Rolf Huisgen* for more than two decades. Some cornerstones of the mechanistic discussion will be reported. Many cycloadditions of these 1,3-dipoles to C=C bonds were performed. It was demonstrated that less electrophilic (*Z*)/(*E*)-isomeric alkenes react stereospecifically, while strongly electrophilic dipolarophiles cross the border to a zwitterionic pathway [90]. Cycloadditions of thiocarbonyl *S*-methylides to thiones unveiled yet another mechanism *via* biradical intermediates. The two-step character of these reactions cannot be recognized by stereochemical investigations, since the dipolarophilic C=S bond lacks a stereochemical marker. Regiochemistry in combination with quantum-chemical calculations provided the evidence. In a density-functional theory (DFT) study on the cycloaddition of unsubstituted thiocarbonyl *S*-methylide to ethylene, no activation energy could be detected for the concerted cycloaddition, showing the 'superdipolarophilic' nature of the C=S bond. The two-step reaction *via* a biradical intermediate proved to be less favorable in this case. The computational evaluation of the cycloaddition of thioacetone *S*-methylide to thioacetone revealed that the energy difference between the still preferred concerted cycloaddition and the biradical pathway decreases on

substitution. Further, it suggested the preferred formation of the 2,4-substituted over the 4,5-substituted 1,3-dithiolane (*Fig. 6*) [91]. These conclusions are in agreement with experimental results on cycloadditions of aliphatic or alicyclic substituted thiocabonyl *S*-methylides to thiones [92]. The preference for the 2,4-substituted 1,3-dithiolane vanishes in favor of the exclusive formation of the 4,5-substituted isomer, when the substituents on 1,3-dipole and dipolarophile are aromatic. Thus, the reaction of thiobenzophenone *S*-methylide with thiobenzophenone gives only 4,4,5,5-tetraphenyl-1,3-dithiolane (*Fig. 7*). A DFT study showed that this result is best explained by formation of a biradical intermediate, which closes to the 4,5-substituted 1,3-dithiolane [93]. A combined experimental and theoretical study on cycloadditions of aliphatic thiocarbonyl *S*-ylides to thiobenzophenone, where synchronous and two-step pathways compete, showed good agreement between experiment and theory [94].

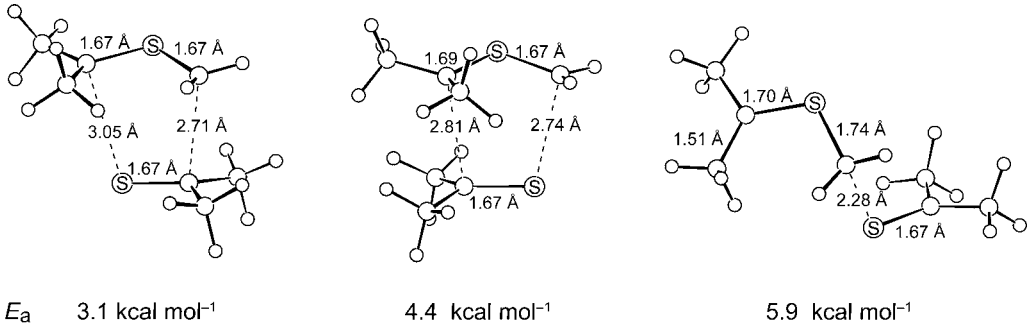



Fig. 6. *Calculated activation energies* ($E_a$) ((U)B3LYP/6-31G*) *for concerted cycloadditions and biradical formation for the reaction of thioacetone* S*-methylide with thioacetone*

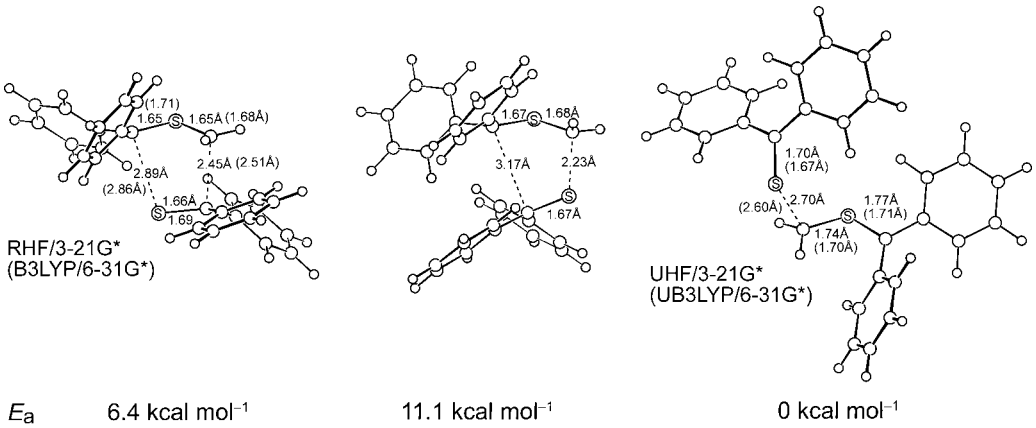



Fig. 7. *Calculated activation energies* ($E_a$) ((U)B3LYP/6-31G*//(U)HF/3-21G*) *for concerted cycloadditions and biradical formation for the reaction of thiobenzophenone* S*-methylide with thiobenzophenone*

While originally the conviction had been that all 1,3-dipolar cycloadditions follow a common synchronous mechanism, evidence has now accumulated that each cycloaddition has to be considered as a unique case. The cycloaddition in question may or

may not be concerted. A continuum of mechanisms seems to be possible. From truly concerted to two-step pathways, the whole spectrum can be realized. The majority of 1,3-dipolar cycloadditions, when analyzed mechanistically, will, however, still follow a concerted ($_{\pi}4_{s} + _{\pi}2_{s}$) pathway. This applies as well to the related ($_{\pi}4_{s} + _{\pi}2_{s}$) *Diels–Alder* cycloaddition [60].

In a recent plenary lecture [95] entitled '*1,3-Dipolar Cycloadditions: Concertedness, Yes or No ?,*' *Rolf Huisgen* displays his present view on the mechanism of these reactions. *Fig. 8* summarizes the ideas; the quotation from the publication presents his present opinion.

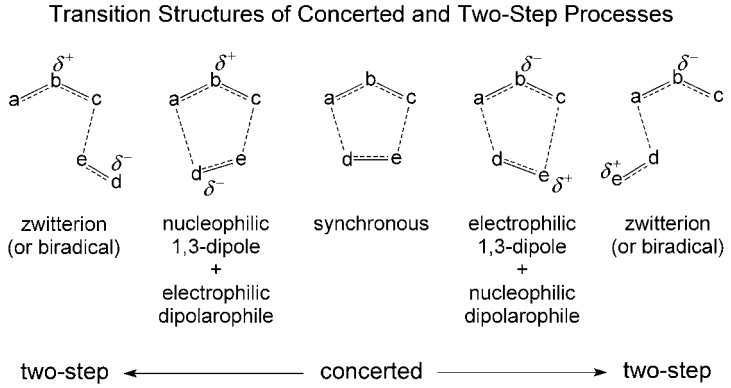



Fig. 8. Huisgen's *view of the possible mechanisms of 1,3-dipolar cycloadditions*

'*Scheme 22* (here *Fig. 8*) *offers a synopsis. The author has no doubts that the majority of* Diels–Alder *reactions and 1,3-dipolar cycloadditions use the concerted pathway. Being allowed by orbital symmetry, these processes profit from low activation enthalpies.*

*The mechanism of 1,3-dipolar cycloadditions can be presented in a string of variations. In the middle stands the synchronous concerted path; in the transition state of this rare case, the two new σ-bonds have the same strength. When reactants are chosen which differ in nucleophilicity and electrophilicity, partial charges occur in the transition state in the sections coming from 1,3-dipole and dipolarophile,* e.g., $\delta^+/\delta^-$ *left of the middle and* $\delta^-/\delta^+$ *right of the middle. The energies of the new σ-bonds and the bond distances in the transition structure differ the more, the higher nucleophilicity and electrophilicity are expressed in the two reactants. In the extremes on the left and the right, the one-step, concerted cycloaddition is superseded by the two-step process* via *zwitterions and biradicals as intermediates.*'

*Rolf Huisgen* merits recognition for having developed the concept of 1,3-dipolar cycloadditions and having made decisive contributions with respect to scope and limitations of these reactions. During the past 50 years, he has had the chance to develop the concept, to uncover many new examples of 1,3-dipoles, and to provide evidence for the mechanistic diversity of these reactions. Already, 20 years ago a two-volume review on these reactions has been published, demonstrating the scope and limitations of 1,3-dipolar cycloadditions, and highlighting the seminal contributions by *Rolf Huisgen* to this synthetically important area of five-membered heterocyclic chemistry.

Readers who want to obtain more detailed information about *Huisgen*'s research efforts and his personal thoughts are advised to study his memoires '*The Adventure Playground of Mechanisms and Novel Reactions*', which we have cited at several occasions in the list of references.

## REFERENCES


[1] H. Wieland, *Liebigs Ann. Chem.* **1934**, *514*, 145; H. Wieland, T. Plötz, H. Indest, *Liebigs Ann. Chem.* **1937**, *532*, 166.
[2] W. Franke, *Naturwissenschaften* **1942**, *30*, 342.
[3] R. Huisgen, *Liebigs Ann. Chem.* **1948**, *559*, 101; R. Huisgen, *Liebigs Ann. Chem.* **1949**, *564*, 16.
[4] R. Huisgen, in 'Methoden der Organischen Chemie (*Houben-Weyl*)', Vol. 3/1, 4th edn., Ed. E. Müller, Georg Thieme Verlag, Stuttgart, 1955, p. 101.
[5] R. Huisgen, 'The Adventure Playground of Mechanisms and Novel Reactions', in 'Profiles, Pathways, and Dreams', Ed. J. I. Seeman, American Chemical Society, Washington DC, 1994, p. XXII.
[6] R. Huisgen, *Angew. Chem.* **1959**, *71*, 5.
[7] J. J. G. Cadogan, in 'Essays on Free Radical Chemistry, Special Publication No. 24', The Chemical Society, Burlington House, 1970, p. 71.
[8] C. Rüchardt, E. Merz, B. Freudenberg, H.-J. Opgenorth, C. C. Tan, R. Werner, in 'Essays on Free Radical Chemistry, Special Publication No. 24', The Chemical Society, Burlington House, London, 1970, p. 51.
[9] R. Huisgen, 'The Adventure Playground of Mechanisms and Novel Reactions', in 'Profiles, Pathways, and Dreams', Ed. J. I. Seeman, American Chemical Society, Washington DC, 1994, p. 15.
[10] H. Wieland, K. Heymann, *Liebigs Ann. Chem.* **1934**, *514*, 145.
[11] W. S. M. Grieve, D. H. Hey, *J. Chem. Soc. (London)* **1934**, 1797.
[12] G. W. Wheland, *J. Am. Chem. Soc.* **1942**, *64*, 900.
[13] R. Huisgen, G. Horeld, *Liebigs Ann. Chem.* **1949**, *562*, 137, and refs. cit. therein.
[14] W. A. Waters, 'The Chemistry of Free Radicals', 2nd edn., Oxford, 1948.
[15] R. Huisgen, 'The Adventure Playground of Mechanisms and Novel Reactions', in 'Profiles, Pathways, and Dreams', Ed. J. I. Seeman, American Chemical Society, Washington, DC, 1994.
[16] R. Huisgen, R. Grashey, *Liebigs Ann. Chem.* **1957**, *607*, 45.
[17] H. Zollinger, in 'Azo and Diazo Chemistry', Interscience Publ., New York, London, 1965, Chapt. 7 and 8; R. Pütter, in 'Methoden der Organischen Chemie (*Houben-Weyl*)', Vol. 10/3, Ed. E. Müller, Georg Thieme Verlag, Stuttgart, 1965, p. 551.
[18] C. Rüchardt, C. C. Tan, *Chem. Ber.* **1970**, *103*, 1774.
[19] C. Rüchardt, E. Merz, *Tetrahedron Lett.* **1964**, 2431.
[20] C. Rüchardt, B. Freudenberg, *Tetrahedron Lett.* **1964**, 3623.
[21] R. Huisgen, H. Nakaten, *Liebigs Ann. Chem.* **1954**, *586*, 84; F. Tröndlin, R. Weerner, C. Rüchardt, *Chem. Ber.* **1978**, *111*, 367.
[22] C. Rüchardt, C. C. Tan, *Angew. Chem., Int. Ed.* **1970**, *9*, 522.
[23] J. J. G. Cadogan, *Acc. Chem. Res.* **1971**, *4*, 186.
[24] R. Huisgen, J. Reinertshofer, *Liebigs Ann. Chem.* **1952**, *575*, 174.
[25] R. Huisgen, J. Reinertshofer, *Liebigs Ann. Chem.* **1952**, *575*, 197; R. Huisgen, H. Reimlinger, *Liebigs Ann. Chem.* **1956**, *599*, 161.
[26] R. Huisgen, H. Reimlinger, *Liebigs Ann. Chem.* **1956**, *599*, 183.
[27] R. Huisgen, 'The Adventure Playground of Mechanisms and Novel Reactions', in 'Profiles, Pathways and Dreams', Ed. J. I. Seeman, American Chemical Society, Washington DC, 1994, p. 23.
[28] R. Huisgen, C. Rüchardt, *Liebigs Ann. Chem.* **1957**, *601*, 21.
[29] R. Huisgen, C. Rüchardt, *Liebigs Ann. Chem.* **1957**, *601*, 1.
[30] R. Huisgen, 'The Adventure Playground of Mechanisms and Novel Reactions', in 'Profiles, Pathways, and Dreams', Ed. J. I. Seeman, American Chemical Society, Washington DC, 1994, p. 22.
[31] J. F. McGarrity, D. P. Cox, *J. Am. Chem. Soc.* **1983**, *105*, 3961.
[32] P. A. S. Smith, 'Open Chain Nitrogen Compounds', W. A. Benjamin Inc., New York, Amsterdam, 1966, Chapt. 10 and 11.
[33] R. Huisgen, 'The Adventure Playground of Mechanisms and Novel Reactions', in 'Profiles, Pathways, and Dreams', Ed. J. I. Seeman, American Chemical Society, Washington DC, 1994, p. 79.
[34] R. Huisgen, *Pure Appl. Chem.* **1989**, *61*, 613, and refs. cit. therein.

[35] E. Wiberg, H. Michaud, *Z. Naturforsch., B* **1954**, *9*, 495.
[36] I. Ugi, H. Perlinger, L. Behringer, *Chem. Ber.* **1958**, *91*, 2324.
[37] J. D. Wallis, J. D. Dunitz, *J. Chem. Soc., Chem. Commun.* **1983**, 910; F. Biesenmeier, U. Müller, W. Massa, *Z. Anorg. Allg. Chem.* **2002**, *628*, 1933.
[38] R. N. Butler, S. Collier, A. F. M. Fleming, *J. Chem. Soc., Perkin Trans. 2* **1996**, 801, and refs. cit. therein.
[39] J. D. Roberts, 'Notes on Molecular Orbital Calculations', W. A. Benjamin Inc., New York, 1962, p. 131.
[40] M. T. Nguyen, T.-K. Ha, *Chem. Ber.* **1996**, *129*, 1157; M. N. Glukchovtsev, H. Jiao, P. v. R. Schleyer, *Inorg. Chem.* **1996**, *35*, 7124; T. M. Klapötke, *Angew. Chem., Int. Ed.* **1999**, *38*, 2536.
[41] J. Sauer, R. Huisgen, *Angew. Chem.* **1960**, *72*, 294.
[42] O. N. Chuphin, V. N. Charushin, H. C. van der Plas, 'Nucleophilic Aromatic Substitution of Hydrogen', Academic Press, New York, 1994
[43] J. F. Bunnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 271.
[44] J. D. Roberts, H. E. Simmons, L. A. Carlsmith, C. W. Vaughan, *J. Am. Chem. Soc.* **1953**, *75*, 3290.
[45] E. F. Jenny, J. D. Roberts, *J. Am. Chem. Soc.* **1955**, *77*, 1248.
[46] A. T. Bottini, J. D. Roberts, *J. Am. Chem. Soc.* **1957**, *79*, 1458.
[47] Review: H. Gilman, J. W. Morton, *Org. React.* **1958**, *8*, 258.
[48] G. Wittig, *Naturwissenschaften* **1942**, *30*, 696.
[49] R. Huisgen, J. Sauer, *Angew. Chem.* **1960**, *72*, 91.
[50] R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes', Verlag Chemie, Weinheim, 1967.
[51] M. Winkler, H. H. Wenk, W. Sander, in 'Reactive Intermediate Chemistry', Eds. R. A. Moss, M. S. Platz, M. Jones Jr., Wiley-Interscience, New York, 2004, p. 741.
[52] R. Huisgen, 'The Adventure Playground of Mechanisms and Novel Reactions', in 'Profiles, Pathways, and Dreams', Ed. J. I. Seeman, American Chemical Society, Washington DC, 1994, p. 70 and refs. cit. therein.
[53] G. Wittig, R. W. Hoffmann, *Chem. Ber.* **1962**, *95*, 2729.
[54] R. Huisgen, R. Knorr, *Tetrahedron Lett.* **1963**, 1017.
[55] R. Willstätter, 'Aus meinem Leben', Verlag Chemie, Weinheim, 1958.
[56] R. Willstätter, E. Waser, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 3423.
[57] W. Reppe, O. Schlichting, K. Klager, T. Toepel, *Liebigs Ann. Chem.* **1948**, *560*, 1.
[58] R. Huisgen, F. Mietzsch, *Angew. Chem., Int. Ed.* **1964**, *3*, 83.
[59] M. B. Bodenstein, *Z. Phys. Chem.* **1913**, *85*, 329.
[60] J. Sauer, R. Sustmann, *Angew. Chem., Int. Ed.* **1980**, *19*, 779, and refs. cit. therein.
[61] R. B. Woodward, R. Hoffmann, *Angew. Chem., Int. Ed.* **1969**, *8*, 781.
[62] E. Vogel, H. Kiefer, W. R. Roth, *Angew. Chem., Int. Ed.* **1964**, *3*, 442.
[63] M. E. Squillacote, A. Bergmann, *J. Org. Chem.* **1986**, *51*, 3911.
[64] J. Sauer, A. Pfeil, G. Schmailzl, unpublished results; G. Schmailzl, Ph.D. thesis, University of Regensburg, 1986; A. Pfeil, Ph.D. thesis, University of Regensburg, 1990.
[65] J. Sauer, *Bull. Soc. Chim. Belg.* **1992**, *101*, 521; J. Sauer, U. Göckel, G. Hennig, J. Reischl, unpublished results; U. Göckel, Ph.D. thesis, University of Regensburg, 1979; G. Hennig, Ph.D. thesis, University of Regensburg, 1982; J. Reischl, Ph.D. thesis, University of Regensburg, 1986.
[66] R. Huisgen, in '1,3-Dipolar Cycloaddition Chemistry, Vol. 1', 1st edn., Ed. A. Padwa, Wiley-Interscience, 1984, p. 1.
[67] A. Padwa, '1,3-Dipolar Cycloaddition Chemistry', 'General Heterocyclic Chemistry Series, Vol. 1, 2', Ed. E. C. Taylor, A. Weissberger, Wiley-Interscience, 1984.
[68] R. Huisgen, *Angew. Chem.* **1955**, *676*, 439.
[69] R. Huisgen, in 'Festschrift zur Zehnjahresfeier des Fonds der Chemischen Industrie', Fonds der Chemischen Industrie, Düsseldorf, 1960, p. 73.
[70] R. Huisgen, *Angew. Chem., Int. Ed.* **1963**, *2*, 565.
[71] R. Huisgen, *Angew. Chem., Int. Ed.* **1963**, *2*, 633.
[72] R. Huisgen, H. Stangl, H. J. Sturm, H. Wagenhofer, *Angew. Chem.* **1961**, *73*, 170.
[73] R. A. Firestone, *J. Org. Chem.* **1968**, *33*, 2285.
[74] R. Huisgen, *J. Org. Chem.* **1968**, *33*, 2291.
[75] W. Bihlmaier, J. Geittner, R. Huisgen, H.-U. Reissig, *Heterocycles* **1978**, *10*, 147.
[76] R. Hoffmann, R. B. Woodward, *J. Am. Chem. Soc.* **1965**, *87*, 2046.
[77] A. Eckell, R. Huisgen, R. Sustmann, G. Wallbilich, D. Grashey, E. Spindler, *Chem. Ber.* **1967**, *100*, 2192.
[78] R. Sustmann, *Pure Appl. Chem.* **1974**, *40*, 569.

[79] K. Fukui, *Bull. Chem. Soc. Jpn.* **1966**, *39*, 498; K. Fukui, *Top. Curr. Chem.* **1970**, *15*, 1; K. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57.
[80] W. v. E. Doering, W. R. Roth, R. Breuckmann, L. Figge, H.-W. Lennartz, W.-D. Fessner, H. Prinzbach, *Chem. Ber.* **1988**, *121*, 1.
[81] R. Huisgen, G. Mloston, E. Langhals, *J. Am. Chem. Soc.* **1986**, *108*, 6401.
[82] R. Huisgen, G. Mloston, E. Langhals, *J. Org. Chem.* **1986**, *51*, 4085.
[83] G. Mloston, E. Langhals, R. Huisgen, *Tetrahedron Lett.* **1989**, *30*, 5373; R. Huisgen, G. Mloston, *Heterocycles* **1990**, *30*, 737; R. Huisgen, in 'Advances in Cycloaddition, Vol. 1', JAI Press Inc., 1988, p. 1.
[84] H. Quast, D. Regnat, E.-M. Peters, K. Peters, H. G. von Schnering, *Angew. Chem., Int. Ed.* **1990**, *29*, 695.
[85] T. Böhm, A. Weber, J. Sauer, *Tetrahedron* **1999**, *55*, 9535.
[86] R. Sustmann, W. Sicking, R. Huisgen, *J. Am. Chem. Soc.* **1995**, *117*, 9679.
[87] R. Huisgen, E. Langhals, *Tetrahedron Lett.* **1989**, *30*, 5369; R. Huisgen, L. Fisera, H. Giera, R. Sustmann, *J. Am. Chem. Soc.* **1995**, *117*, 9671; L. Fisera, R. Huisgen, I. Kalwinsch, E. Langhals, X. Li, G. Mloston, K. Polborn, W. Sicking, R. Sustmann, *Pure Appl. Chem.* **1996**, *68*, 789.
[88] U. Rohr, J. Schatz, J. Sauer, *Eur. J. Org. Chem.* **1998**, 2875.
[89] I. Kalwinsch, L. Xingya, J. Gottstein, R. Huisgen, *J. Am. Chem. Soc.* **1981**, *103*, 7032.
[90] R. Huisgen, X. Li, H. Giera, E. Langhals, *Helv. Chim. Acta* **2001**, *84*, 981; R. Huisgen, G. Mloston, H. Giera, E. Langhals, *Tetrahedron* **2002**, *58*, 507; G. Mloston, R. Huisgen, H. Giera, *Tetrahedron* **2002**, *58*, 4185; H. Giera, R. Huisgen, E. Langhals, K. Polborn, *Helv. Chim. Acta* **2002**, *85*, 1523; R. Huisgen, G. Mloston, E. Langhals, T. Oshima, *Helv. Chim. Acta* **2002**, *85*, 2668.
[91] R. Sustmann, W. Sicking, R. Huisgen, *Chem.–Eur. J.* **2003**, *9*, 2245.
[92] R. Huisgen, G. Mloston, K. Polborn, R. Sustmann, *Chem.–Eur. J.* **2003**, *9*, 2256.
[93] R. Sustmann, W. Sicking, R. Huisgen, *J. Am. Chem. Soc.* **2003**, *125*, 14425.
[94] R. Huisgen, G. Mloston, H. Giera, E. Langhals, K. Polborn, R. Sustmann, *Eur. J. Org. Chem.* **2005**, *8*, 1519; R. Sustmann, W. Sicking, R. Huisgen, *Eur. J. Org. Chem.* **2005**, *8*, 1505.
[95] R. Huisgen, in 'Chemistry and Biological Applications of Oxygen- and Sulfur-Containing Heterocycles', Ed. V. G. Kartsev, IBS Press, Moscow, 2003, p. 83.

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