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DISCOVERIES MISSED, DISCOVERIES MADE: CREATIVITY, INFLUENCE, AND FAME IN CHEMISTRY

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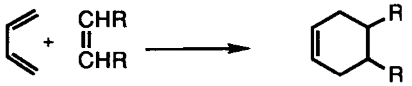
Abstract—The paper describes some of the historical background of the discoveries of the diene synthesis and the orbital symmetry conservation rules. It examines the circumstances that prevented these discoveries from being made by earlier investigators and speculates about the mental qualities conducive to creativity in science.

Discovery in science evolves from the interactions of personality, history, and happenstance. By clarifying the patterns of influence, we gain insight into how the human mind works. Perhaps, by thus sharpening our sensitivities, we may improve our own chances of becoming discoverers. Even if not, by scrutiny of the ideas, true and false, of our illustrious predecessors, we may at least enhance our own strengths and compensate for our weaknesses.

With these objectives in mind, I describe here two case histories of major discoveries in organic chemistry, the Diels–Alder 'diene synthesis' and the Woodward–Hoffmann orbital symmetry rules. In these accounts, the missed opportunities have as much to teach us as the final successes.

DIELS, ALDER, THEIR COMPETITORS, AND THE DISCOVERY OF THE DIENE SYNTHESIS

The formation of a cyclohexene by the conjugate addition of a 1,3-diene and an alkene (Scheme I), which has come to be called the diene synthesis or Diels–Alder reaction, has few rivals among the transformations of organic molecules for general applicability in synthesis and deep mechanistic implication.[1]



Scheme I.

Diels and Alder themselves in their first paper in 1928[2] immediately grasped the significance of their work, both theoretical and synthetic:

> Our results will play a role not only in the discussion of theoretically interesting questions, for example, the relationships of strain in polycyclic systems, but probably also will yield greater significance in a practical sense. Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has been moved to the near prospect.

With unmistakable severity, they issued a warning to would-be interlopers to stay out of the field they obviously now considered their own:

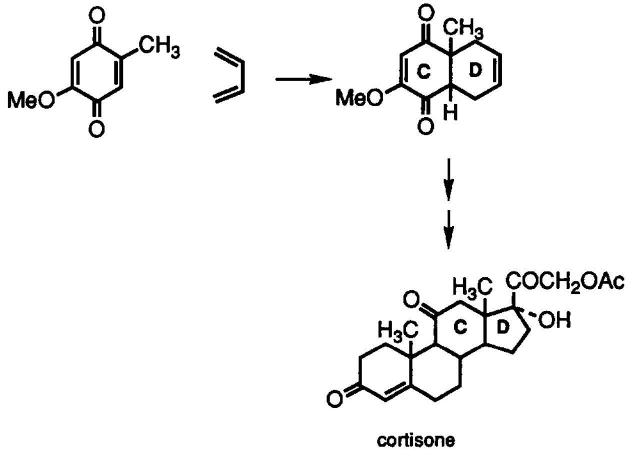
> We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems.

Some inkling of the fierce territoriality they felt is evident in their chastisement[3] of Farmer and Warren,[4] who had had the temerity to question the [4+2] nature of the addition:

> We take the view that the authors would have done better to have written one of us a private letter expressing their request and to have withheld the publication of their paper until the appearance of our thoroughgoing third contribution, which was then in press and has since appeared.
>
> Since we are engaged in filling the last holes in the understanding of the course of the diene synthesis, we direct to Messrs. Farmer and Warren the urgent request to disregard those events which obviously fall in the domain of the addition reactions we are studying.

Diels and Alder were right, of course, in the sense that their reaction did prove to be profoundly significant in the synthesis of natural products. It is just as well, however, that their claim of exclusive ownership came to be ignored by the rest of the chemical community, since they themselves made only minor contributions to natural product synthesis using their discovery. The reasons for this would take another paper to explore but probably include the distractions provided by the inexhaustible richness of the mechanistic and stereochemical questions associated with the diene addition, which occupied them in the 1930s and 1940s, Alder's discovery of the ene reaction, which diverted his attention even further, and the advent of World War II, which completely disrupted normal research in Germany. The first major moves toward the modern fulfillment of Diels and Alder's prediction came more than twenty years later, in the early 1950s, with applications in the Woodward[5] and Sarett[6] total syntheses of cortisone and in the Stork[7] synthesis of cantharidin. In the Woodward design for cortisone, for example, even the casual reader could sense the arrival of new thinking about synthesis and could not escape the attraction of the compelling story that began with the first step, a Diels–Alder reaction between methoxytoluquinone and butadiene (Scheme II). The product incorporated functional groups for eventual elaboration to rings C and D of the cortisone structure.

The profound significance of the diene synthesis was recognized by the award of the 1950 Nobel Prize in Chemistry jointly to Diels and Alder "for their discovery and development of the diene synthesis".



Scheme II.

PREDECESSORS AND NEAR-DISCOVERERS

Diels and Alder were not the first to observe a cyclohexene-forming diene–alkene cycloaddition. How did it happen that they emerged with the credit for this brilliant discovery? What I have to offer on this question depends heavily on conjecture, but there are a few clues. If we follow them, we may glimpse the interaction of forces and events that led to that outcome.

As early as 1892, Zincke had found,[8,9] and later correctly formulated,[10,11] a dimer of tetrachlorocyclopentadienone, and Lebedev[12] recognized vinylcyclohexene as the dimer of butadiene. It is perhaps not surprising that neither of these workers realized the generality of the process.

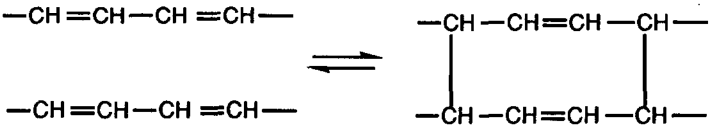
Zincke's observation had been a side issue in his exploration of other unrelated phenomena. The reaction itself occurred under conditions in which the product was not stable, and its presence could be inferred only indirectly. Zincke did well to unravel a complicated story and had no obvious basis for discerning this particular golden nugget embedded in the hard rock of difficult but routine investigation.

Lebedev was a participant in a controversy over the mechanism of formation of rubber (formally a polymer of isoprene) and other natural polymers. His attention and that of contemporaries such as Staudinger[13] and Harries[14] was directed elsewhere. (We should say 'misdirected', since of course we now know, with the arrogance of our posteriority, that the ordinary thermal dimerization of aliphatic 1,3-dienes has nothing to do with the formation of natural rubber).

von Euler and a near miss

Well then, were there others in a better position to have discovered the [4+2] cycloaddition before Diels and Alder? The answer is yes. And here the determinative influence of personal circumstance begins to manifest itself. In Diels and Alder's first paper,[2] they refer to the work of von Euler and Josephson,[15] who begin their account with the words

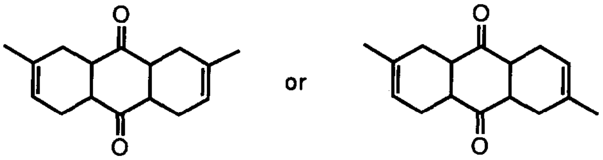
> In connection with not yet published studies on the course of the condensation of isoprene to rubber, one of us has approached more closely the question of how the group of atoms —CH=CH—CH=CH— reacts with other unsaturated groups, in which the goal of the study was, at least in favorable cases, a numerical value for the equilibrium (Scheme III):



Scheme III.

> The necessary preliminary work has led to some new results of preparative significance.

von Euler and Josephson proceeded to describe their observation of a 2 : 1 adduct of isoprene and *p*-quinone. Based essentially on two facts, namely the formation of a tetrabromide and a dioxime, they assigned the structure(s) shown in Scheme IV:



Scheme IV.

They realized that their job of structure proof was incomplete and talked their way out of it:

> Because one of us had to interrupt the foregoing investigation, the reduction study has not yet been resumed; it will take place soon.

This promise was never to be fulfilled.

Clearly recognizing that they were onto something important, they pointed out that the structures they proposed

> contain the assumption that each of the isoprene molecules uses one valence of the terminal carbon atoms, and both inside free valences saturate themselves by formation of a 2,3-double bond. This is completely in accord with the experience of conjugated double bonds.

At this point, it is difficult to suppress the feeling that von Euler, at the very threshold of opportunity, turned and walked away. He and Josephson had the diene addition in their hands eight years before Diels and Alder! They had the correct structure of the adduct. They fully understood the mechanistic implication of their results as a manifestation of conjugate addition. And yet they never published another word on the subject. Why would a chemist give up a project of this significance apparently to pursue another task? Actually, who was Hans von Euler, and what was the other project that diverted his attention at this crucial moment?

From a biographical notice by Wilhelm Franke, *On Hans von Euler's 80th Birthday*[16] we learn that he was (and had been since 1906, when he was 33 years old) Ordinarius Professor of General and Organic Chemistry at the University of Stockholm. Josephson was his student. von Euler was to become director of the Biochemical Institute at that university in 1929, the same year that he shared the Nobel Prize in Chemistry (with A. Harden) for investigations on the fermentations of sugars and the fermentative enzymes.

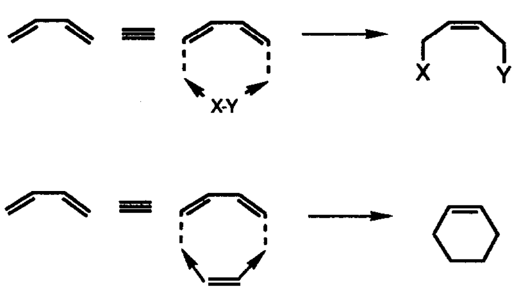
Although he worked in Sweden for most of his life, von Euler was German—to the core. The son of a Bavarian military officer, he served Germany in both World Wars, in the first as a flyer and in the second with duties specified only as being "on the Turkish front". Franke seems to suggest that von Euler's conduct in World War II was acceptable, since it was not politically motivated but rather based upon the moral stance of the soldier. Nevertheless, despite a number of expiatory actions by von Euler, many of his Swedish countrymen never forgave him his willing service to the German regime.

Be that as it may, there is no doubt that von Euler was a fabulous scientist, one of the most versatile and creative of the century. He was trained as a physical chemist, studying at one time or another with Landolt, Nernst, van't Hoff, and Arrhenius. He also became adept at organic chemistry as a result of brief but influential stays in the laboratories of Hantzsch and of Thiele (of whom more in a moment). Probably under the influence of Arrhenius, von Euler became increasingly drawn toward biochemistry, and by 1910 was already started on the monumental series of studies of enzyme structure, kinetics, and mechanism that were to make him world-famous. What is astonishing is that while all this was going on, he was somehow able to find time for occasional forays into pure organic chemistry. This dazzling little thrust in 1920 with Josephson on the isoprene–quinone reaction was just one of many half-finished studies he seemed to toss off, as it were, almost for amusement.

We now can understand why von Euler could walk away from the discovery of the diene synthesis. He was deeply engaged in another massive project that had developed into his real life's work. It would be irresponsible to permit a mere, although seductively promising, diversion to interfere. In other words, von Euler did not have time to spend winning the Nobel Prize for the diene synthesis. He was too busy winning it for enzyme mechanisms.

Nevertheless, von Euler's ready use of the idea of conjugate addition stimulates another line of thought. Although the von Euler–Josephson paper does not refer to the source of information on what they called "the experience of conjugated double bonds", it seems certain that they had in mind the extensive studies by von Euler's former mentor Thiele in the 1890s, which had led to the idea of 'partial valence'. In fact, Thiele himself, the guru of conjugated systems, would have been a likely candidate to become the discoverer of the diene synthesis. How much of a leap of the imagination would it have required, after all, for the man who had established conjugate addition of dienes to several reagents (X–Y) to realize that a similar addition to alkenes should occur? (Scheme V, opposite).

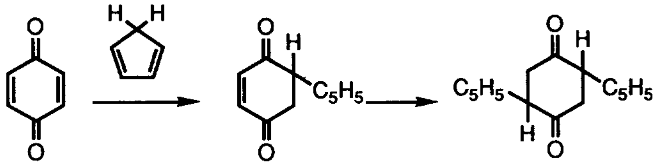
Although Diels and Alder's 1928 paper[2] does not refer directly to Thiele's work as a forerunner of their own, the authors do emphasize that the diene addition amounts to reaction of the free valences at the 1,4-positions of the diene, an idea so widely associated with Thiele that they probably felt a reference unnecessary. So we have the inevitable question: Why did Thiele not discover the diene synthesis?



Scheme V.

The mystery of Albrecht

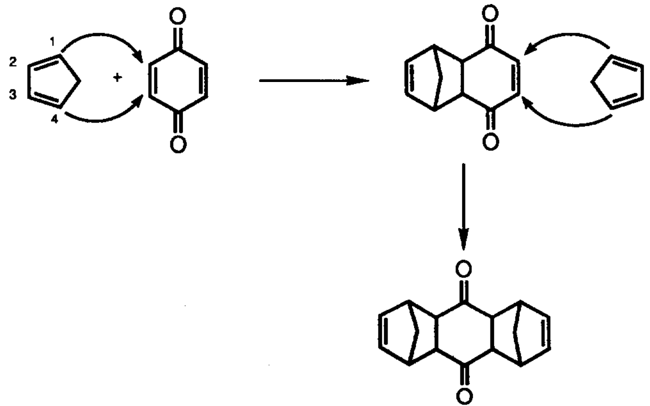
To approach the answer, we must start by examining a paper of 1906 by Albrecht,[17a] which is reference 1 in the 1928 Diels–Alder paper. In fact, Albrecht's interpretation of his experimental results is a major target of the Diels–Alder paper. Albrecht had reported that the reaction of cyclopentadiene and quinone had given both a 1 : 1 and a 2 : 1 adduct. He was quite diffident about the structures of these and stated that the properties could not be reconciled with any probable structure, although he did write tentative formulas (Scheme VI):



Scheme VI.

These represented the products to be expected if a C—H bond of cyclopentadiene added to a C═C double bond of quinone.

Diels and Alder proceeded to show experimentally that the mono adduct and the diadduct had only two C═C double bonds each, rather than the three and four, respectively, that Albrecht's structures contained. They re-formulated the reactions as 1,4-conjugate additions giving bridged polycyclic structures (Scheme VII):



Scheme VII.

In view of the moderate and almost apologetic claims Albrecht had made, the tone of the Diels–Alder criticism of his paper was harsher than one might have thought absolutely necessary. It may be that the territorial imperative was manifesting itself here also.

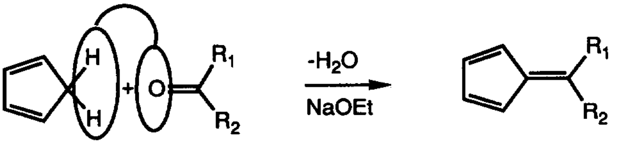
In any case, a superficial reading of Albrecht's paper[17a] leaves the impression that, with the handicap of the relatively undeveloped state of organic chemistry in 1906, he simply did not have the vision that Diels and Alder were able to bring to bear upon the problem 22 years later. But a closer examination reveals some puzzling questions.

Why had Albrecht been working on the reaction of cyclopentadiene and quinone in the first place? The introduction to the paper,[17a] where one might have expected to find a stated reason (or at least a rationalization), is curiously blunt and uninformative. The first sentence reads merely: "Cyclopentadiene adds to one or two moles of quinone with extreme ease merely upon mixing, to give beautifully crystalline, stable compounds". Moreover, the heading of the paper gives no date of receipt of the manuscript and no indication of the laboratory where the work had been done. The latter omission perhaps is not surprising, since naming the originating laboratory did not become common until somewhat later in the century. Presumably in 1906, the names of the major researchers alone were sufficient identification and carried with them the well known facts of their location. But Albrecht was not a major researcher. In the decade following 1906, Chemical Abstracts does not list a single publication under his name. So we have another question: Who was Walther Albrecht?

A strong hint of an answer is given by a footnoted reference[17b,18] in the Diels–Alder paper to Albrecht's "*Über Cyclopentadienequinone.* Inaugural Dissertation, München, 1902". Apparently, Albrecht had been a graduate student at Munich in the years just before 1902, and the work reported in his 1906 paper[17a] must have been taken from his dissertation. Oddly, Albrecht's paper gives no acknowledgment to his research advisor, but a moment's reflection leaves little doubt that it must have been . . . *Thiele*!

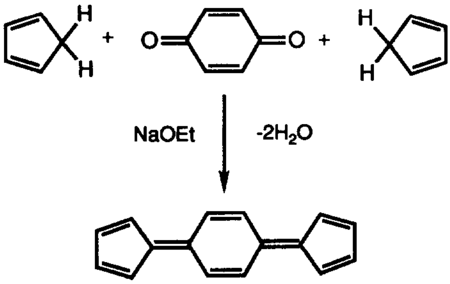
Thiele

Johannes Thiele had come to Munich in 1893, and by 1890, the major part of his work on conjugate additions had been completed. Now he was heavily engaged in the synthesis and study of the fulvenes, which were highly reactive, colored compounds of great interest as potential synthetic building blocks and also as vehicles for the study of theories of color and constitution. Fulvenes were made by the condensation of cyclopentadiene with aldehydes or ketones (Scheme VIII):



Scheme VIII.

It is a reasonable conjecture that Thiele was fascinated with the prospect of synthesizing a double fulvene by condensation of two moles of cyclopentadiene with the conjugated diketone quinone (Scheme IX):



Scheme IX.

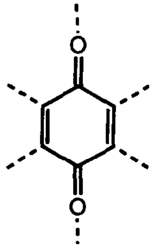
None of this is forthcoming from Albrecht's laconic paper, but a hint that it is probably true comes from a paper by Thiele and Balhorn[19] in the very same issue of the Annalen. This article deals with the synthesis of several fulvenes. It does not refer to Albrecht's paper, but footnote 1 is an acknowledgment: "Several of the substances described in the following were prepared by Mr. W. Albrecht". The clinching evidence comes from Albrecht's dissertation itself,[17b] the acknowledgement of which is to Thiele.

The first paragraph of the dissertation tells the whole story:

> Thiele has condensed cyclopentadiene with aldehydes, ketones, and carboxylic esters to fulvene derivatives, intensely colored compounds, which arise by elimination of water. Occupied with the elaboration of these compounds, I tested the behavior of cyclopentadiene toward quinones and found that benzoquinone reacts vigorously with the hydrocarbon. The two compounds combine without elimination of water.

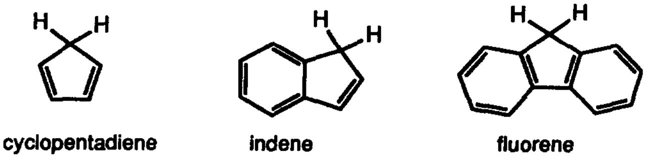
The experimental section describes the conditions for carrying out the addition, which consist merely of mixing the components together neat, or more controllably, in an inert solvent. These conditions are quite different from the ones established by Thiele for making fulvenes, which always used sodium ethoxide as a 'condensing agent'. Today, we recognize that the function of the base was to convert cyclopentadiene to its anion. Although Albrecht's thesis contains no mention of it, I think it is highly likely that the base-mediated conditions must have been at least discussed by the professor and his student and probably tried in the cyclopentadiene–quinone reaction. It is my conjecture that this approach was abandoned because of the competing decomposition of quinone itself in basic medium. Given the primitive state of mechanistic understanding at the time, it would not be surprising if Albrecht had simply tried to carry out the reaction without the condensing agent. Once products had been obtained, the reigning theory of the laboratory, namely Thiele's ideas of partial valence, dominated the interpretation. Thus, quoting Thiele,[20] Albrecht argues[17b]

> In accord with its unsaturated nature, quinone is an extraordinarily reactive substance and is especially distinguished by its lively tendency to add hydrogen and substances with labile hydrogen. It contains a system of cross-conjugated double bonds. This leads to free partial valences not only at the terminal O-atoms, but also at the four inner C-atoms, so that it invites addition at not less than six points of attack, as is shown in the following structural formula (Scheme X):



Scheme X.

> Cyclopentadiene condenses with aldehydes, ketones, and oxalic ester. The C═C double bonds evidently cause a loosening effect on the neighboring methylene group similar to that of C═O double bond in ketones.
>
> The reactivity in condensation of indene is somewhat diminished and that of fluorene is significantly diminished relative to that of cyclopentadiene (Scheme XI). Evidently the partial valences that influence the CH_2 group in cyclopentadiene are saturated within the attached benzene rings, thereby reducing the loosening effect on the methylene groups and the condensation reactivity.

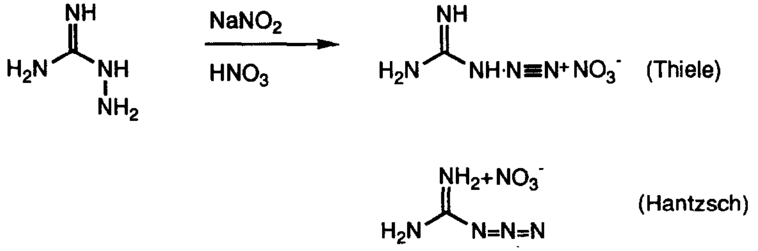


Scheme XI.

Of course, these ideas do not explain why cyclopentadiene reacts by *condensation* (with elimination of water) with other ketones but reacts by *addition* with quinone. It seems reasonable to speculate that Thiele was quite disappointed with the outcome of Albrecht's experiments. Thiele must have hoped for the 'usual' cyclopentadiene condensation reaction, which would have given the spectacular double fulvene. I assume that when the results did not conform, Thiele wanted nothing more to do with the project and gave permission to Albrecht to publish the facts, but without Thiele's name on the paper. Apparently, Thiele in his own mind had gone beyond his conjugate addition phase; now he was thinking condensation. His failure to make this little mental jump back to addition reminds us of an iron law of science: a discovery is both a finding and a recognition of the finding. Thiele and Albrecht had fulfilled only half of the requirement. Thiele died in 1918 and so never had to endure the knowledge that the credit for what would have been the crowning manifestation of his partial valence theory ultimately would fall to others.

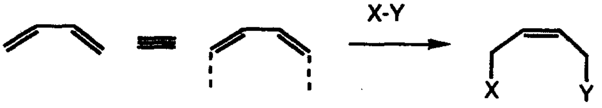
Was Thiele's inaction here due to a momentary slip of attention uncharacteristic of the man, or was his nature such that, great chemist though he was, these disappointments were likely, predictable, even fateful? We cannot be sure, but what his contemporaries write about him is at least consistent with the latter hypothesis. I offer thoughts on Thiele taken from the autobiography of Richard Willstätter.[21] A number of the factual details and some of the most important of the personal evaluations are corroborated in an obituary notice by Fritz Straus.[22]

> At Easter time, 1893, Baeyer called Johannes Thiele as the successor to E. Bamberger in the new position of Extraordinary Professor. As a student of Volhard, barely a year past his habitation in Halle, he had become known for his excellent preparative work on guanidine derivatives. Nitroguanidine gave by reduction aminoguanidine and subsequently by the action of nitrous acid something very striking: diazoguanidinium nitrate, a remarkable aliphatic diazonium compound. At least so it appeared. It is a puzzle how it escaped the widely knowledgeable and keenly thoughtful author and his contemporaries for many years that this was simply the conversion of an acid hydrazide to an acid azide, exactly as Curtius had transformed countless acid hydrazides to acid azides. Much later, Hantzsch brought to view the surprising and simple explanation.



Scheme XII.

> It seems to me that Thiele—in the style of the scientists after Baeyer—was more gifted to command than to listen.
>
> The young Thiele was a powerful presence. He took over the position of head of the organic department, for which no tradition existed, and he made a model installation of it. Whereas the students had had no contact with his predecessor Bamberger, Thiele taught and ruled the laboratory and the student body with a new liveliness and sense of community. The combustion analyses were improved, the requirements in preparative training were raised, the students were stimulated and compelled to experiment with test tubes, dozens of which were kept clean in drawers and had to be filled in exactly prescribed ways. Doctoral candidates in greater numbers were graduated with well chosen and well guided dissertation projects. Military discipline ruled. And the students liked and respected this unfamiliar rule.
>
> Thiele divided his time between the general laboratory and his small private laboratory. He visited not only his own co-workers but also, especially in the first years, every beginner. Also the lecture course, alternating great lectures on benzene derivatives and coal tar dyestuffs, corresponded to a high level of instruction.
>
> Among Thiele's scientific accomplishments during his time in Munich, the series of studies on conjugated double bonds is prominent. It was a great thought, supported by refined experiments, that a system of neighboring double bonds exhibits partial affinity and consequently adds in the 1,4-positions (Scheme XIII):



Scheme XIII.

A weakness of the work, which later led to some disillusionment, lay only in the generalization that these systems *must* add at the ends. In truth, the unsaturated system can add this way, but there exist other cases of addition at adjacent carbon atoms. One of the most beautiful results was a new interpretation of the Kekulé benzene formula by Thiele, the assumption that the partial affinities of the three double bonds in a ring completely saturate themselves (Scheme XIV):

Scheme XIV.

Thiele's work on conjugated systems made him famous in his time. His theory of partial valence was one of the most sophisticated of the pre-electronic attempts to understand the relationship between structure and reactivity. Eventually, of course, we must agree with the evaluation of Walter Hückel:[23]

> While it is quite true that today this hypothesis must be regarded as obsolete and superseded, a short presentation thereof will nevertheless be given at this point, first of all because the hypothesis of partial valences has played an important role in the historical development of organic chemistry, and secondly because in it can be seen most clearly the limits set to the primitively visualizable (mechanistic) representations of the chemical behavior of organic compounds, and finally also, because this hypothesis did nevertheless enable us to foresee somewhat, or hazard a guess, as to what has today, though in a somewhat changed form, assumed real shape.

Willstätter's reminiscences continue:

> From this first day until his departure nine years later, I co-existed respectfully with Thiele, with great interest in his personality and his scientific achievements. He developed and changed quickly. He was from the Silesian border region, indeed not German-looking, short and very broad and thickset and after a few years very corpulent. With heavy tread he went around through the labs slamming the doors behind him. He was a reserve lieutenant and a mountain-climber. His friend Käswurm, a herculean figure, dragged him along up several peaks. But his increasing obesity soon brought his performance of military service and his mountain sport to an end.
>
> In the first years Thiele prepared his lectures and his work with freshness and industry, in the next he committed his extraordinary powers to the great investigations of unsaturated systems. Then he began to become sluggish and tired early as a researcher.
>
> In Thiele, the privatdozent and the student had before their eyes a model teacher and department head, who was there for his students and was dedicated to his job, who was a master of organic chemistry, and who possessed the eye and the hand of a chemist. He was scientifically versatile, but he wanted nothing to do with compounds of an unknown and complex sort. To puzzling natural products he had an actual aversion.
>
> Thiele declined an offer from Greifswald. In a meeting of the privatdozent group, the physiologist Cremer, son-in-law of the influential opthalmologist von Rothmund, expressed the opinion that this was "A fatal stupidity. For a position as Ordinariat, I would crawl on my knees over all of Germany". Only much later, in the winter semester of 1901–2, did there come another offer, which was favorable and prestigious. It was a call to Strasbourg, with which Thiele was overjoyed. At this time the thirty-seven-year-old man was no longer a worker. He avoided the students and no longer was interested in his private laboratory.
>
> In the following period at Strasbourg, Thiele was a respected professor, who led his institute well. But his crop already had been harvested. I encountered him at the jubilee of the University of Berlin in the fall of 1910, where he represented the rector of his university and I the Federal Institute of Technology (E.T.H.). But I was troubled to see this important man slacken again. In the World War, he found a military occupation as a censor. Toward the end of his life, he threw his own correspondence under his clothes chest. Thiele was spared the experience of the loss of Strasbourg. The ascent to the heights and the beginning of his decline came in the time of his nine years in Munich. Was the cause of his alteration that Thiele

> lacked the strength to correct his mistakes, or did the weakness of this strong man, that he could not admit error, bring about the early conclusion of his scientific development? Toward the end of his time in Munich, Thiele encountered important examples of additions that did not follow his rule of 1,4-addition and in fact contradicted his published experimental statements. These results were difficult for Thiele to bear. They were never published.

Although his personality and background would not naturally have drawn him close to Thiele, Willstätter clearly felt tremendous respect and admiration for his colleague. Nevertheless, Willstätter cast a cold eye on those of Thiele's deficiencies that ultimately arrested his scientific growth. One wonders whether it would have been in vain to offer these criticisms to the suffering Thiele directly. Would they have been received with enough objectivity to have benefitted him? Probably not. Few of us have the courage or self-confidence to give or to receive such advice. But the insights into Thiele's character we have just read support the idea that his formulaic, systematic way of thinking about science was not the right intellectual equipment to cope effectively with the unexpected. Doing science at the highest, most creative level is a bit like playing jazz. One has to be disciplined, yes, but also open, flexible, ready to abandon an idea and pick up a new one when Nature thrusts it upon one.

As luck would have it, Willstätter's book contains a remarkable photograph of the Munich organic chemistry research group in 1901. In addition to the great Baeyer himself, surrounded by his associates, it shows several other members of the faculty, including Koenigs, Einhorn, Willstätter, and Thiele. There also is a picture of the young Jakob Meisenheimer, a student of Thiele, who was

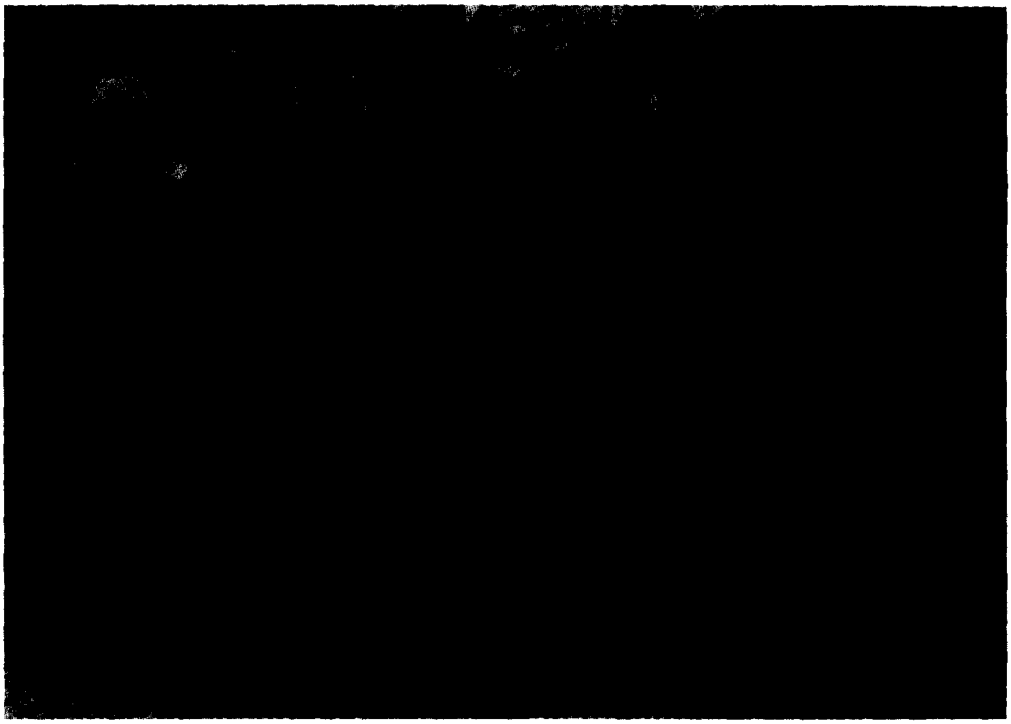


Fig. 1. A photograph of research workers at the Chemical Institute of the University of Munich in 1901. Professor Baeyer sits in the front row holding his hat. On his right is Professor Koenigs, and seated on his immediate left is Professor Thiele. Professor Einhorn is on Thiele's left. Wilstätter is the bearded man standing just beyond Baeyer's right shoulder, and to his immediate right, in a lab apron, is Meisenheimer. Albrecht is the clean-shaven young man with a bow tie, hair parted in the middle, two rows straight back from Wilstätter. *Taken from Table VII of Wilstätter's book (reference 21) and reproduced with permission of Verlag Chemie.*

to become a renowned professor in his own right. Several names are listed without initials. No doubt these are graduate students, a conjecture that receives some support from their modest placement in the rear of this distinguished company. Among them we find the once-mysterious Albrecht. Given the timing of this event, it seems likely that when the photography session ended, he may well have returned directly to his lab bench to continue his work on the cyclopentadiene–quinone reaction.

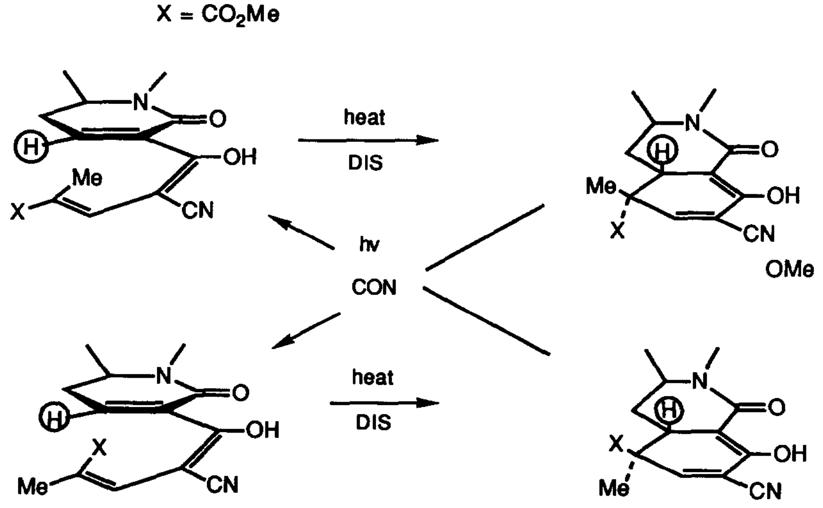
Were this a world of pure logic, Thiele rightfully should have been the discoverer of the diene synthesis. There even seems to be irony in the near-homophonous names of the discoverers and the near-discoverers: Diels–Alder/Thiele–Albrecht. Probably we ask too much if we insist that when his window of opportunity opened in 1902, Thiele should have made the mental connection that would have been necessary. Unusual insight would have been required to do that so early. On the other hand, as we have seen, there was a stiffness in his thinking that might have prevented him from ever seeing the answer. Perhaps it is fair to say of this, with Cassius, "the fault, dear Brutus, is not in our stars, but in ourselves".

THE ALTERNATION EFFECT AND THE DISCOVERY OF ORBITAL SYMMETRY CONSERVATION

In 1981, the Royal Swedish Academy of Sciences, recognizing work carried out in the 1950s and 1960s, awarded Nobel Prizes in Chemistry to Kenichi Fukui of Kyoto University and Roald Hoffmann of Cornell University "for their theories, developed independently, concerning the course of chemical reactions". Hoffmann had collaborated closely with Robert Burns Woodward of Harvard University. Although Woodward already was a Nobel Laureate for other work, few chemists doubt that had he lived, his contributions to this field would have placed him again in Stockholm, alongside Fukui and Hoffmann.

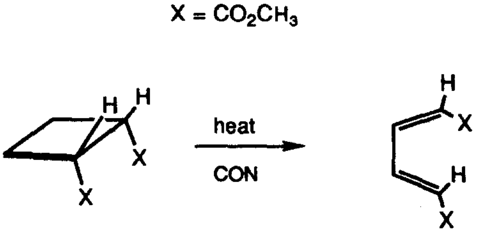
Experimental stimulus for the orbital symmetry rules

The Nobel citations mention 'theories', but it is well to keep in mind that, at least the Woodward–Hoffmann work was driven in the first instance by experiment. No one tells this story as well as Woodward himself. His account,[24a] rich in characteristic darts, feints, digressions, paradoxes, puzzles, and jocularities, is too long for us to repeat here, but we can focus on the original motivation, which was the synthesis of a dauntingly complex molecule, Vitamin B_{12}. Woodward describes the observation of the peculiar pattern of behavior of the synthetic intermediates shown here (in partial structures, Scheme XV):



Scheme XV.

Note that the ring-closure or opening is *disrotatory* in the thermal reactions and *conrotatory* in the photochemical reactions. Moreover, Woodward and Hoffmann recalled that some years before, Vogel[25] had reported the highly stereospecific thermal ring-opening of dimethyl cyclobutane-*cis*-3,4-dicarboxylate to dimethyl *cis, trans*-muconate (Scheme XVI).



Scheme XVI.

Now here comes a crucial insight. The thermal cyclization of the triene system in the Vitamin B_{12} synthesis is cleanly *disrotatory*, but the thermal decyclization in Vogel's compound is cleanly *conrotatory*. Woodward says:[24a]

> Here then we were faced with a most remarkable situation; two obviously closely related processes, each of them occurring with essentially complete stereospecificity, but in each case the stereospecificity was precisely the opposite, that is, in the cyclobutene opening the conrotatory mode was followed, while in the formation of cyclohexadiene from the open-chain triene a disrotatory process was cleanly followed. It now seemed certain to us that there must be a very fundamental factor at work in these reactions, and it was not long before we discerned that there might be a correlation between these facts and the symmetries of the molecular orbitals of the π-systems involved.

Theory

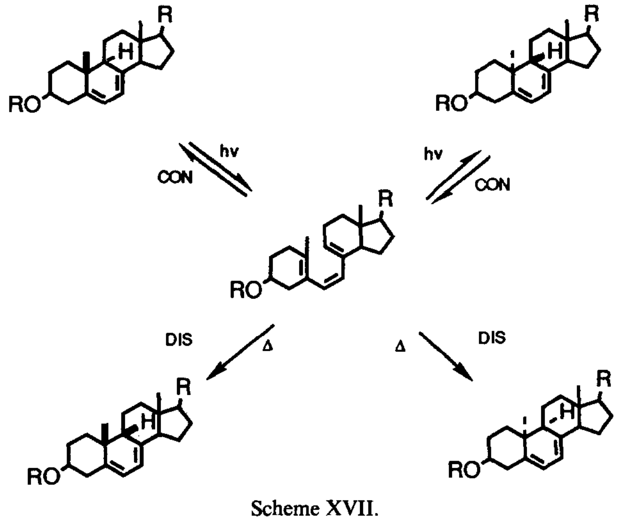
The experimental observation is that there is an *alternation* of the conrotatory and disrotatory modes, with the determining factor being the *number* of π-electron centers in the linear polyene chain. In thermal reactions, four such centers give conrotation and six give disrotation. The basic theoretical idea is that this alternation is caused by the alternation of the symmetry and antisymmetry of the molecular orbitals of linear polyenes.[26] The stereochemical course of the reaction is held to be controlled by the symmetry or antisymmetry of the highest occupied molecular orbital.

This also offers an explanation for the switch from disrotatory *thermal* reaction to conrotatory *photochemical* reaction observed in the triene system of the Vitamin B_{12} intermediate. On the assumption that the first excited state of a photochemical reactant is the one actually undergoing reaction, the highest occupied orbital would be of opposite symmetry to that of the ground state molecule, and a simple extension of the rule would predict exactly the observed change.

These ideas were first put into print in a series of short communications in 1965.[24b–d] In bold and sweeping extrapolations, Woodward and Hoffmann elaborated them to cover a wide range of other kinds of so-called concerted pericyclic reactions, including many that had not yet been observed. Confirmatory experimental evidence supporting many of the predictions soon came, and this kind of theoretical analysis became commonplace in the literature.

Predecessors: Havinga, Schlatmann, Oosterhoff

Nevertheless, the alternation effect that produces opposite stereospecificities for thermal and photochemical cyclizations of linear polyenes had been observed prior to Woodward's Vitamin B_{12} work, as Woodward and Hoffmann pointed out. In carefully documented studies by Havinga and Schlatmann at Leiden, reported in 1961,[27] the triene shown here exhibited exactly the same preference for photochemical conrotation and thermal disrotation (Scheme XVII):



Scheme XVII.

Havinga and Schlatmann considered several explanations of this behavior but did not arrive at a definite hypothesis. Two sentences near the end of the paper, however, refer to personal discussions with Oosterhoff. These took on great significance in the aftermath of the Woodward–Hoffmann orbital symmetry excitement four years later:

> As Prof. Oosterhoff pointed out, another factor that possibly contributes to the stereochemical difference between the thermal and photo induced ring closure may be found in the symmetry characteristics of the highest occupied π-orbital of the conjugated hexatriene system. In the photo excited state this highest occupied orbital is antisymmetric with regard to the plane that is perpendicular to the bond 6,7 making *syn* approach less favourable.

Oosterhoff was an outstanding theoretical physical organic chemist at Leiden, a logical person to have solved this problem. In fact, in a sense it might be said that he did solve it, for his explanation, although apparently offered with considerable diffidence, was essentially the same as that of Woodward and Hoffman's main idea. Why then did Oosterhoff not follow up on his insight? Why did he not extrapolate and generalize from it and cause a revolution in the way chemists think about reaction mechanisms?

It is my conjecture that the reason was that Oosterhoff thought that the explanation was oversimplified if not actually wrong.[28] He said as much in a conversation at the Bürgenstock Conference on Stereochemistry in 1966. With his sophistication about photochemistry, he recognized that it was by no means obvious that the photochemically active state in these reactions was the first excited state, as Woodward and Hoffman had postulated. To him, it seemed likely that the mechanism was more complicated, especially since, as Dauben[29] had pointed out, the ground state of cyclobutene is about 20 kcal/mole less stable than that of butadiene, and therefore the spectroscopic singlet of cyclobutene is about 50–60 kcal/mole higher than that for butadiene. A direct transformation of the butadiene first excited state into the cyclobutene first excited state, as envisioned by Woodward and Hoffmann, therefore would be energetically improbable.

Oosterhoff worried and worried at this question, and in 1968, he and his student van der Lugt produced a paper[30] based upon valence bond theoretical calculations that gave a definitive answer. Their results are summarized in the state diagram (Fig. 2). This demonstrates the energies of the ground state and the first two excited states of butadiene and cyclobutene as functions of an angle, whose value is a short-hand way of tracking the extent of progress along the reaction coordinate. Note that in accord with the Woodward–Hoffmann rules, the ground state strongly prefers the

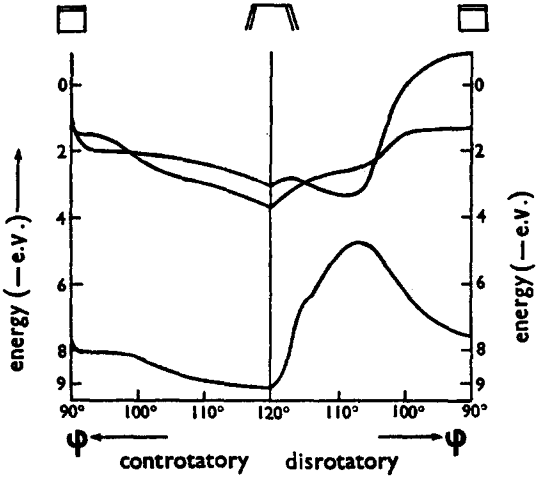


Fig. 2. Energies of the ground state and two excited states during the cyclization of 1,3-butadiene to cyclobutene. *Taken from reference* 30 *and reproduced with permission of the Royal Society of Chemistry.*

conrotatory pathway. The lowest energy photoexcited state at the planar butadiene geometry (Franck–Condon transition) is the antisymmetric one, but in the disrotatory pathway headed toward cyclobutene, this state makes an 'intended' crossing with higher-lying but rapidly descending symmetric excited state. In nuclear configurations lacking two-fold symmetry, these states mix, and the crossing is avoided, leading to emergence of the symmetric state at lower energy than the antisymmetric one. This rather deep well or funnel occurs (necessarily, according to Oosterhoff's theory) close in geometry to the ground state energy maximum characteristic of a Woodward–Hoffmann 'forbidden' reaction. Passage then to the symmetric ground state surface occurs by a radiationless process. The overall result is that disrotation is preferred, in agreement with experiment,[31] but the excited state involved is not that assumed in the original orbital symmetry formulation.

It is entirely understandable that a mind as penetrating as Oosterhoff's could not let go of this challenging problem until a solution had been found. The beauty and depth of his analysis are undeniable. Moreover, the idea of a reaction funnel created by close energetic and geometric approach of an excited state minimum and a ground state maximum has great significance for the understanding of photochemical reactions. Yet it must be said that Oosterhoff, in pursuing this puzzle to its resolution, allowed himself to be diverted from the even more significant implications of the alternation effect.

CONCLUSIONS

Thiele's intellectual rigidity and defensiveness would not permit him to take the one little step he needed to add the diene–alkene reaction to the list of conjugate additions he already had discovered. Oosterhoff's keen insight and mental toughness drove him to the solution of the funnel problem but forbade him from making the broad but (in his view) unacceptably approximate generalizations that would have led to the orbital symmetry theory. Putting aside the circumstantial differences of the two cases, one might say, without intending disrespect to two great chemists, that the near-misses in the recognition of the diene synthesis and of the orbital symmetry theory had in common a certain failure of the imagination.

The lesson for the working scientist in these stories is one we already know, whether or not we have articulated it to ourselves: The defining property, which is also the immutable precondition, of creativity is the proper conflation of rational and imaginative elements. One needs the right blend of order, discipline, and clarity with ardor and unfettered fantasy. One must reconcile the old idealized polarities of human intellection—the classical with the romantic, the apollonian with the dionysian. Perhaps even the vast majority of us whose creative powers are modest can benefit if we recognize the need for this balance.

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