grams should be continued and expanded in areas considered as new frontiers. Second, and more important for near-term energy demands, hydrologic studies of deep sedimentary basins should be made in areas of high subsurface temperatures to locate zones of fluid saturation and enhanced permeabilities as an aid in selecting drill sites. These studies should be followed by a major drilling and pump testing program in areas where a population center coincides with these three favorable geologic conditions (heat, water, and enhanced permeability). Such a program could be initiated immediately and could produce results that may be beneficial to 20 of the 30 eastern states. A phased program could call for drilling to begin in 1981 on the most favorable resource areas, with all attractive areas assessed by 1986.

Such a plan has recently been developed (*29*). The program called for in the plan is not costly. It could be done in conjunction with other programs of exploratory drilling, for example, the Eastern Gas Shales Project, continental drilling, and waste disposal. Personnel of the state geologic surveys could perform much of the work during their basic data-gathering programs. Costs could be shared by potential users. However, federal funding, organization, and stimulation could help guarantee a systematic approach. The exploratory drilling program should then be followed immediately by a demonstration project at a key resource area to help remove operational, legal, and other impediments to development. It would be important for the demonstration to deal with all legal and environmental requirements to clear the way for further developments by private enterprise.

Conclusions

This general discussion identifies some of the evidence of hydrothermal or geothermal resources in many of the central and eastern parts of the United States. Enough evidence exists to warrant a thorough investigation of this potential. The economic attractiveness and national need for domestic energy sources justify the need for such an exploratory program.

To fairly evaluate the resource, it will be necessary that many wells be drilled; this drilling must be preceded or accompanied by a series of geologic, geophysical, and hydrologic tests. This is the only way that some of the risks attendant upon the development of these reservoirs can be removed. After identifying favorable resources through the drilling program, the remaining impediments to development can be reduced through the experience gained from a demonstration project in which the resource is used for residential or industrial space (or process) heating.

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From Diyls to Ylides to My Idyll

Georg Wittig

Chemical research and mountaineering have much in common. If the goal or the summit is to be reached, both initiative and determination as well as perseverance are required. But after the hard work it is a great joy to be at the goal or the peak with its splendid panorama. However, especially in chemical research—as far as new territory is concerned—the results may sometimes be quite different: they may be disappointing or delightful. Looking back at my work in scientific research, I will confine this talk to the positive results (*1*).

Some 50 years ago I was fascinated by an idea which I investigated experimentally. The question was how ring strain acts on a ring if an accumulation of phenyl groups at two neighboring carbon atoms weakens the C-C linkage and predisposes to the formation of a diradical (for brevity called diyl) (Fig. 1). Among the many experimental results (*2*) I choose the synthesis of the hydrocarbons **1** and **4** (*3*), which we thought capable of diyl formation. Starting materials were appropriate dicarboxylic esters, which we transformed into the corresponding glycols. While these were obtained under the influence of phenylmagnesium halide only in modest yield,

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phenyllithium proved to be superior and was readily accessible by the method of K. Ziegler, using bromobenzene and lithium. The glycolates resulting from the reaction with potassium phenylisopropylide formed—on heating with methyl iodide—the corresponding dimethyl ethers, which supplied the equivalent hydrocarbons **1** and **4** by alkali metal splitting and demetalation with tetramethylethylene dibromide.

The resulting tetraphenylbenzocyclobutane (**1**), however, rearranged to triphenyldihydroanthracene (**3**) (Fig. 2). In contrast, tetraphenyldihydrophenanthrene (**4**), which was prepared analogously, proved to be a stable hydrocarbon, even when substituents R were introduced that forced the biphenyl system to twist. While **4** did not decompose at 340°C and was stable in solution against oxygen, its aryl-weakened C-C bond could be observed since it split with potassium into the ring-opened dipotassium derivate. The results of these investigations on formation of radicals and ring strain seem to indicate that ring closure is more likely to contribute to stabilization of the ethane bond.

This stabilizing influence is documented impressively by the behavior of tris(biphenylene)ethane (**7**), which was also synthesized (*4*) (Fig. 3). The carbinol **6**, which was formed by the reaction of the ketone **5** with *o*-lithiobiphenyl, transformed into the desired hydrocarbon **7** by an acid-catalyzed twofold Wagner-Meerwein rearrangement.

This first aromatic propellane, which melted at 475°C without decomposition and whose structure agreed with the nuclear magnetic resonance spectrum, proved to be insensitive to ethane linkage-breaking sodium-potassium alloy. Evidently the close aryl packing prevents penetration of the metal into the interior of the molecule.

Since the tendency to form diradicals was not evident with the hydrocarbons mentioned, we intended to replace the phenyl groups by anisyls. Therefore, suitable dicarboxylic esters should be brought into reaction with *p*-lithioanisole (*5*). But, as we obtained unexpected smears, the functionally simple benzophenone was used to treat the mixture that resulted from the reaction of *p*-bromoanisole with lithium. Instead of the expected *p*-anisyldiphenylcarbinol, the bromine-containing compound **9** was isolated, whose structure could be proved by conversion into the well-characterized derivative by zinc dust distillation. Accordingly, *p*-lithioanisole, which was originally formed, metalates the *p*-bromoanisole that is still present into compound **8**, which then reacts with benzophenone to form the isolated compound **9** (Fig. 4).

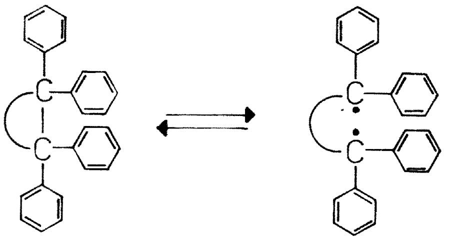


Fig. 1. Formation of a diradical (*2*).

When it was noted that phenyllithium too can modify *p*-bromoanisole to form **9**, we decided to look closer at the lability of the aromatic proton as a function of the substituent. In the course of these studies we arrived at the surprising result that aryl iodide, bromide, and even chloride can exchange with the electropositive metal of phenyllithium (*6*). Later we called this principle of reaction *umpolung*, or reversal of polarity (*7*) (Fig. 5). Simultaneously and independently, H. Gilman found the same behavior when treating aryl halides with butyllithium.

Among the halogens of the various aromatic systems, fluorine proved to be not exchangeable with lithium (*8*). Here we found an unexpected reaction path. First we observed that in the formation of biphenyl by the reaction of monohalobenzene with phenyllithium, fluorobenzene acted rapidly, forming approximately 75 percent biphenyl, while the other halobenzenes produced only 5 to 7 percent. We interpreted this result as indicating that biphenyl formation was preceded by metalation of the halobenzene, which was stimulated by the inductive effect of the strongly electronegative fluorine. This explanation was supported by the finding that not biphenyl but *o*-

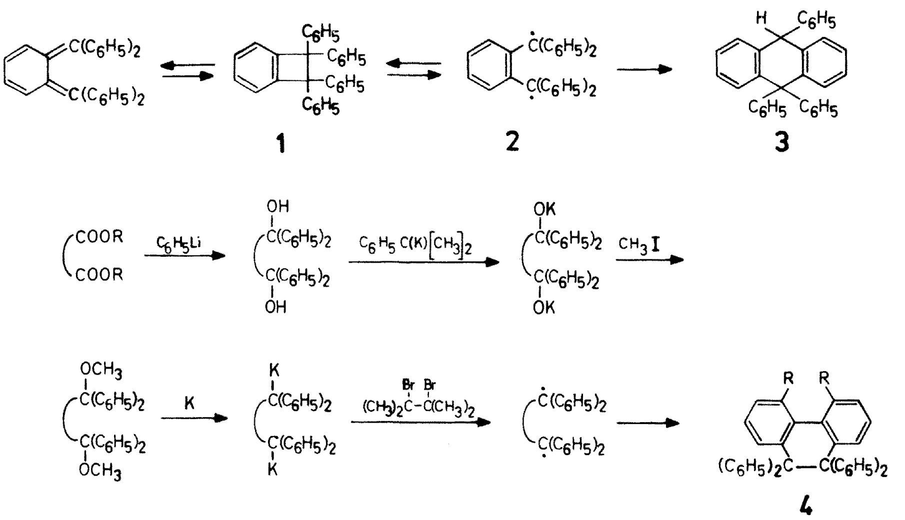


Fig. 2. Some reactions observed in the synthesis of **1** and **4** (*3*).

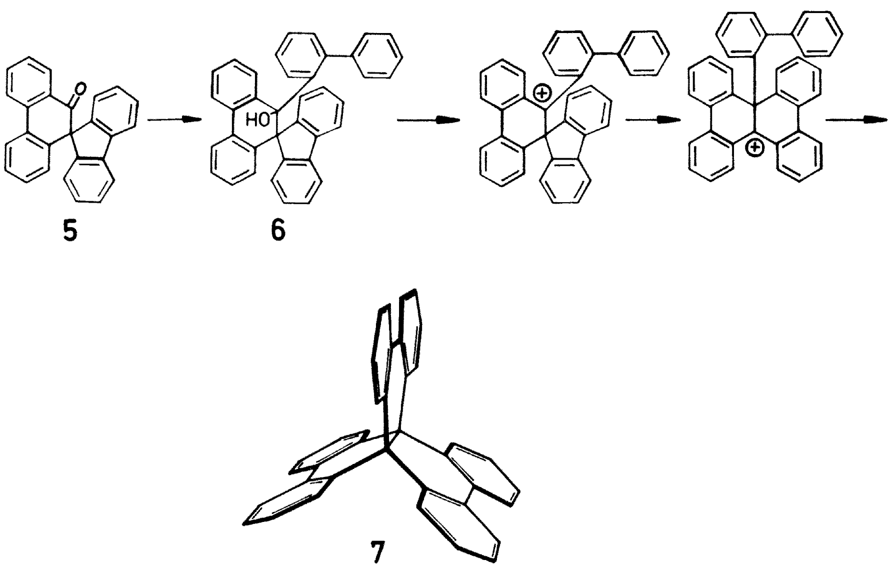
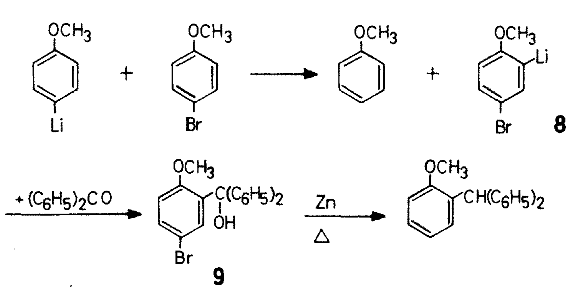


Fig. 3. Formation of tris(biphenylene)ethane (*4*).



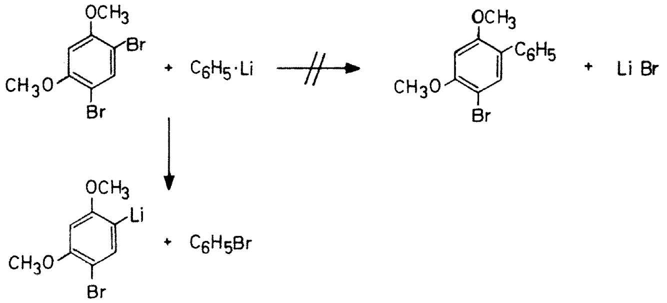
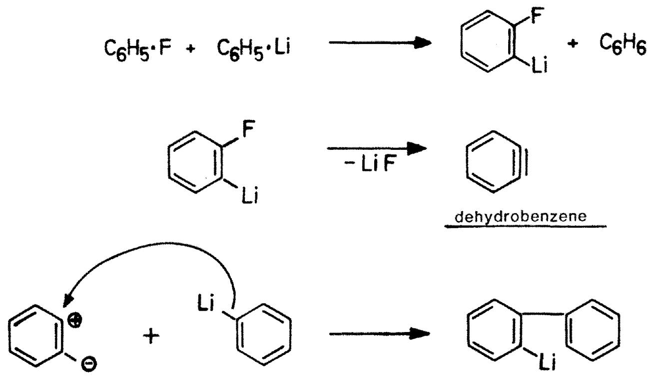


Fig. 4 (left). Formation and characterization of compound 9 (*5*). Fig. 5 (right). Reversal of polarity (*umpolung*) (*6*).



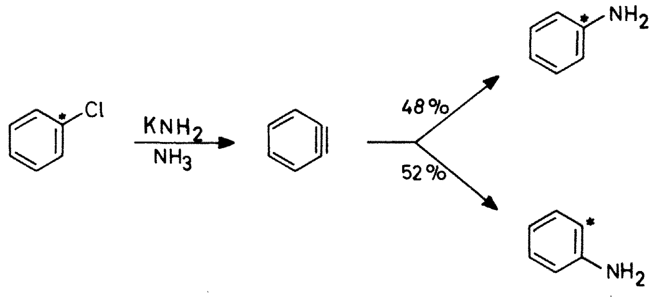


Fig. 6 (left). Mechanism of formation of *o*-lithiobiphenyl (*8*, *9*). Fig. 7 (right). Proof of the intermediate occurrence of dehydrobenzene in the reaction of ^{14}C-labeled chlorobenzene with potassium amide in liquid ammonia (*10*, *24*).

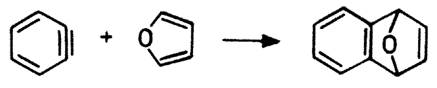


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Fig. 8. Proof of the existence of dehydrobenzene through the formation of **10** (*11*).

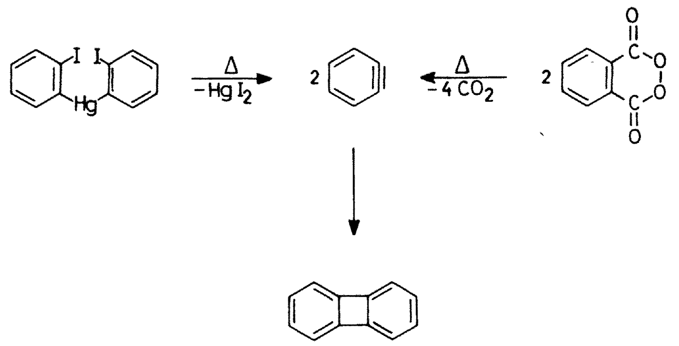
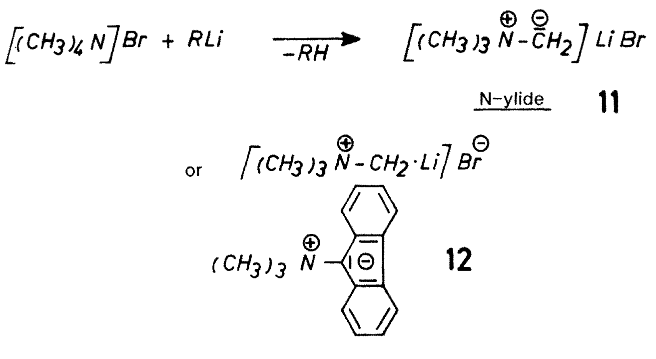
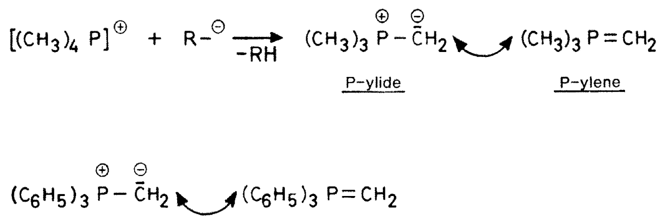


Fig. 9. Thermal decomposition reactions used to determine the lifetime of dehydrobenzene in the gas phase (*12*).



$$[(CH_3)_4N]Br + RLi \xrightarrow[-RH]{} [(CH_3)_3\overset{\oplus}{N}-\overset{\ominus}{C}H_2]\,LiBr$$

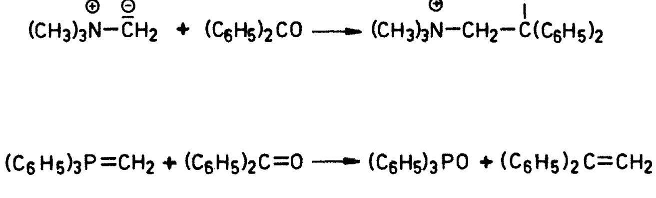
$$\text{or}\quad [(CH_3)_3\overset{\oplus}{N}-CH_2\cdot Li]\,\overset{\ominus}{Br}$$



$$[(CH_3)_4P]^{\oplus} + R^{\ominus} \xrightarrow[-RH]{} (CH_3)_3\overset{\oplus}{P}-\overset{\ominus}{C}H_2 \leftrightarrow (CH_3)_3P{=}CH_2$$

$$(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H_2 \leftrightarrow (C_6H_5)_3P{=}CH_2$$

Fig. 10 (left). Formation of *N*-ylides (*13*). Fig. 11 (right). Formation of *P*-ylides (*17*).



$$(CH_3)_3\overset{\oplus}{N}-\overset{\ominus}{C}H_2 + (C_6H_5)_2CO \longrightarrow (CH_3)_3\overset{\oplus}{N}-CH_2-\overset{O^{\ominus}}{\overset{|}{C}}(C_6H_5)_2$$

$$(C_6H_5)_3P{=}CH_2 + (C_6H_5)_2C{=}O \longrightarrow (C_6H_5)_3PO + (C_6H_5)_2C{=}CH_2$$

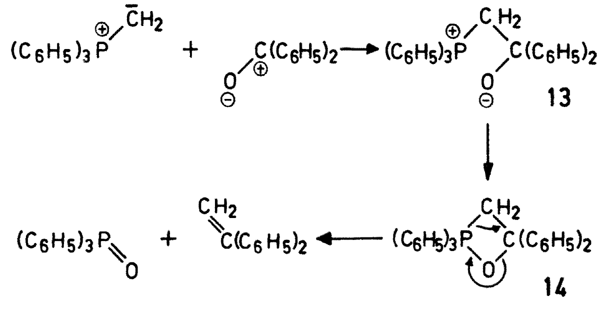


Fig. 12 (left). Reactions with benzophenone (*18-20*). Fig. 13 (right). Steps in the reaction of triphenylphosphinemethylene with benzophenone (*25*).

lithiobiphenyl had been produced. In 1942 we further assumed that an elimination of metal and halogen results that leads to the occurrence of dehydrobenzene (*9*), and this is what changes phenyllithium into the *o*-lithiobiphenyl found experimentally (Fig. 6). Independent of our work, a proof for the intermediate occurrence of dehydrobenzene was given by Roberts *et al.* (*10*), who reacted [1-^{14}C]chlorobenzene with potassium amide in liquid ammonia and isolated the two expected anilines with approximately 50 percent yield (Fig. 7).

Later we could prove the existence of the dehydrobenzene by expecting that it would react as dienophile (*11*). For the diene and solvent we chose furan, which, being an ether, should favor organometallic exchange while simultaneously serving as a trapping agent. In an exciting experiment we had *o*-fluorobromobenzene react with lithium amalgam in furan and isolated with good yield the endo-oxide **10**, which had been formed by a Diels-Alder addition (Fig. 8).

We found the lifetime of dehydrobenzene in the gas phase (*12*) by the thermal decomposition of bis(*o*-iodophenyl)mercury as well as phthaloyl peroxide to biphenylene at 600°C in an argon atmosphere at reduced pressure. When furan was injected behind the decomposition zone naphthol was evolved as a by-product from the dihydronaphthalene endoxide that occurred first. Under the conditions used, the lifetime of dehydrobenzene was determined to be 20 milliseconds. See Fig. 9.

Phenyllithium, which had opened so many areas by acting as a sort of dowsing rod, was applied many times in the course of our research. Now our attention was drawn to the proton-labile substrates, to the aliphatic as well as the aromatic ones.

The process of proton-metal cation exchange appeared to us to be of fundamental importance, since the electron density at the carbon atom is enhanced after metalation. Thus the question arose of how carbanions, with their negative charge, would behave compared to carbonium ions, with their positively charged carbon atoms.

At the time we were not sure whether hydrogen bound to carbon would be proton-labile in quaternary ammonium salts. We came to this conclusion with an absurd experiment to prepare pentamethylnitrogen from tetramethylammonium salts by using the reaction of tetramethylammonium halide with methyllithium (*13*).

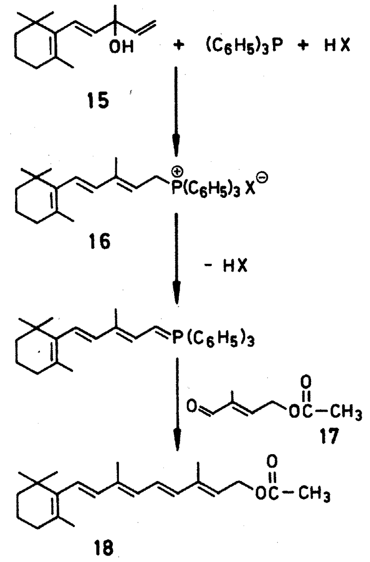


Fig. 14. Formation of vitamin A acetate (*22*).

$(C_6H_5)_3B + C_6H_5Na \rightleftharpoons [(C_6H_5)_4B]Na$

Fig. 15. Addition of phenylsodium to triphenylboron (*26*).

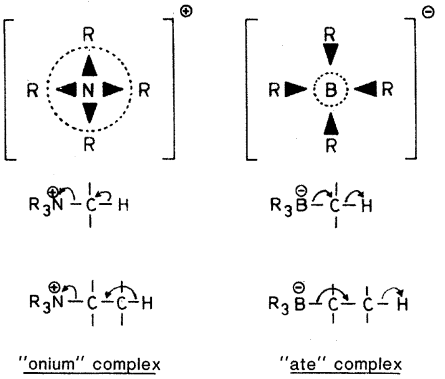


Fig. 16. Comparison of "onium" and "ate" complexes (*23*).

It was confirmed experimentally that the octet principle is strictly valid for the elements of the first eight-element period. The object of synthesizing compounds with a pentacoordinate central atom was reached only when we studied the higher elements of the fifth main group—that is, phosphorus, arsenic, antimony, and bismuth. It was easy to synthesize their pentaphenyl derivatives (*14*) and, in the case of antimony, also pentamethylantimony, which (as a nonpolar compound) is a liquid with a boiling point of 126°C (*15*).

Tetramethylammonium chloride reacting with methyl- or phenyllithium loses one proton and forms a product that we called trimethylammonium methylide (*11*) (Fig. 10). We gave the name *N*-ylides to this new class of substances since the bonding of the carbon to the neighboring nitrogen is homopolar (yl) and ionic (ide) at the same time. Trimethylammonium fluorenylide (*12*) could be isolated salt-free, thus its ylide structure is unambiguous (*16*). Subsequently, ylides as well as cryptoylides were studied more thoroughly (*17*).

When we extended this concept to the phosphonium salts, we found that they could be converted into the corresponding *P*-ylides even more readily than the analogous ammonium salts when treated with organolithium compounds (Fig. 11). The reason for the greater proton mobility is that phosphorus, unlike nitrogen, can expand its outer electron shell to a decet. This allows an energy-lowering resonance stability between the ylide and ylene forms.

In the case of the *N*-ylide the semipolar nature of the N-C bond is demonstrated by its ability to add to benzophenone, forming the well-defined betaine (*18*) (Fig. 12). Now, if the same reaction was performed with triphenylphosphinemethylene, the expected betaine adduct was not obtained but, astonishingly, triphenylphosphine oxide and 1,1-diphenylethylene (*19*). Evidently the initially produced betaine **13**—due to the ability of the central atom to expand its electron shell—formed the four-membered ring **14**, which then decayed into two fragments as final products (*20*) and could not be isolated by itself (Fig. 13).

That the first step of the reaction is betaine formation was shown with the reaction of triphenylphosphinemethylene and benzaldehyde. In this case the betaine could be isolated as an intermediate product, and it decayed to triphenylphosphine oxide and styrene only on heating (*20*). This type of reaction (*21*) seemed to be of fundamental importance for preparative chemistry, and it also found industrial application (*22*). By these means it was possible to prepare vitamin A and *β*-carotene, among others. In the present context I restrict the discussion to the synthesis of vitamin A, which is produced industrially at BASF under the direction of Pommer (*22*). The phosphonium salt **16**, obtainable from vinyl-*β*-ionol **15**, triphenylphosphine, and acid, changes with HX splitting into the corresponding phosphinemethylene derivative, which reacts with *γ*-formylcrotylacetate **17** to produce vitamin A in the form of its acetate **18** (Fig. 14).

With the addition of phenylsodium to triphenylboron, it could be demonstrated that boron can also act as tetracoordinate central atom (Fig. 15). Today this complex serves as an analytic reagent for the determination of potassium, rubidium, and cesium ions as well as for the quantitative determination and separation of ammonium and alkaloid salts.

We called the complex salts with negatively charged central atom "ate" complexes for understandable reasons (*23*). They can be compared with the "onium" complexes, which were already known, as shown in Fig. 16. Because of the inductive effect of the central atom in onium complexes, all ligands R are cationically labilized and the hydrogen atoms at the neighboring carbon atoms are proton-mobile; however, in ate complexes all ligands at the central atom are anionically labilized and the hydrogen atoms at the neighboring carbon atoms are hydride-labile. This rule explains numerous reactions. I do not have time here to discuss its importance as a heuristic principle.

Thus I come to the end of my lecture. The excursion from diyls to ylides now ends at my idyll. With this I mean the conclusion of my research work as an emeritus, which allowed me to continue my work as a chemist free from the obligations of a teacher, and finally to devote myself completely to my interest in fine arts. I want to close my talk by offering cordial thanks to my collaborators. Without them my work could not have been accomplished.

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DNA Methylation and Gene Function

Aharon Razin and Arthur D. Riggs

Summary. In most higher organisms, DNA is modified after synthesis by the enzymatic conversion of many cytosine residues to 5-methylcytosine. For several years, control of gene activity by DNA methylation has been recognized as a logically attractive possibility, but experimental support has proved elusive. However, there is now reason to believe, from recent studies, that DNA methylation is a key element in the hierarchy of control mechanisms that govern vertebrate gene function and differentiation.

The methylated base 5-methylcytosine (m^5Cyt) (Fig. 1) was discovered in calf thymus DNA about 30 years ago (*1*). Since then, the occurrence of this minor base has been demonstrated in a wide variety of organisms, including all vertebrates and plants that have been studied (*2*). In mammalian DNA, 2 to 7 percent (depending on the species) of the total cytosine is converted to m^5Cyt (*3*). Methylation occurs enzymatically after DNA synthesis by methyl transfer from *S*-adenosylmethionine (SAM) to position 5 of cytosine (*4*).

In vertebrates, m^5Cyt is the only modified base yet found in DNA. The biological role of m^5Cyt in eukaryotic DNA is not known, but its ubiquity suggests some important function. In the last decade, several hypotheses suggesting a role of m^5Cyt in gene regulation have been advanced (*5*-*8*). However, there has been only one review on m^5Cyt in eukaryotic DNA (*9*), and this review was completed before the power of restriction enzyme analysis was fully realized. Studies of the last 2 years, mainly with restriction enzymes, have drastically changed the experimental approaches to a solution of the long-standing enigma of the function of m^5Cyt in eukaryotic DNA. The purpose of this article is to review critically the available information in this rapidly expanding field. It will be obvious that we prefer the idea that m^5Cyt is involved in gene regulation and differentiation, but its involvement in other possible functions will also be considered.

Protein-DNA Interactions

Regardless of the details, it has long been our opinion (*6*) that the essential function of m^5Cyt is to modify protein-DNA interactions. The conversion of cytosine to m^5Cyt introduces a methyl group into an exposed position in the major groove of the DNA helix (Fig. 2), and the binding to DNA of proteins such as the lac repressor, histones, and hormone receptors is known to be affected by changes in the major groove (*10*). For example, it has been shown (*11*) that changing the thymine residue at nucleotide position 13 in the lac operator to uracil or to cytosine greatly decreases the affinity of repressor for operator. Changing position 13 to m^5Cyt restores the affinity for repressor to normal. Therefore, the lac repressor only senses the presence or absence of a methyl group at position 13. Bacterial restriction enzymes have a strong affinity for unmethylated restriction sites, but have a reduced affinity for, and no activity on, methylated sites (*12*-*14*). Thus, it is a solid fact that m^5Cyt can profoundly affect the binding of proteins to DNA. The only question is whether

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