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ADVANCES IN CANCER RESEARCH

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ADVANCES IN CANCER RESEARCH

Volume I

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PREFACE

Cancer is a disease which has been recognized since ancient times, and which in every generation has claimed many victims of all ages and of all stations in life. Each generation through its medical practitioners has fought it with whatever ideas and tools were available at the time. It is a paradox that, as these ideas have become ever more clear and these tools ever more powerful, the proportion of individuals dying of cancer appears to have risen from year to year. Whatever the reason for these melancholy statistics may be, no matter whether they may be more apparent than real, it is not in the tradition of science to stand idly by in the face of this seeming failure. A society living in the midst of scientific miracles may rightly expect that this disease, like many others, should be comprehended and mastered.

Although the comprehension and the successful therapy of a disease are not invariably related, it is the hope of rational men, confident in the scientific method, that if only a phenomenon were understood it could be controlled. Few more notable expressions of this faith in our time are evident than in the public and private support granted in many lands to the subject and field of cancer research. A host of scientific specialties has been marshaled to meet this challenge. As the search for the understanding of cancer proceeds, new scientific approaches develop and are emphasized, and older ones, for the time being perhaps, subside and diminish. The ebb and flow of ideas and experimental approaches in the field of cancer research, as in any of the creative areas of the arts and sciences, is a mysterious and inexplicable process.

It is the purpose of the Editors that this and succeeding volumes of this series shall reflect this steady and inevitable march of the tides of our knowledge and increasing understanding. For this task, we must rely upon the generous cooperation of our colleagues in many lands, distinguished authorities in various branches of cancer research, to review, synthesize, and interpret the advances made in their individual areas of investigation. It is our hope that these pages will reveal from year to year the gallant and dedicated quest for comprehension and mastery of an ancient and elusive disease.

THE EDITORS

January, 1953

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Electronic Configuration and Carcinogenesis

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I. Introduction

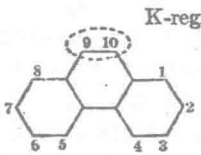
This account of the possible relationship between electronic configuration and carcinogenesis falls naturally into six sections. These are: (1) historical survey, (2) the quantum-mechanical resonance method of describing large unsaturated molecules, (3) the alternative molecular-orbital method, (4) numerical applications of these two methods, (5) possible mechanisms of carcinogenic activity, and (6) conclusions. Of these (2) and (3) are not solely concerned with carcinogenic properties, but no reasonably simple and straightforward account of the two methods discussed seems to be available. This is particularly important if we bear in mind that both methods are approximations, whose reliability is not fully established. We shall see that although there is a considerable measure of mutual agreement, there are several places in which they disagree. As a result of this, there is still a certain amount of personal liberty possible in the interpretation of the calculations. Indeed, it may be admitted at once that no final or complete account of the relation between electronic configuration and carcinogenesis has, or can, yet be given. The present account will therefore attempt to stress both the undoubted successes of the theory and at the same time some of its equally patent inadequacies. The whole field is a singularly interesting one, because it represents one of the very first serious attempts to relate what are obviously complex biological phenomena to quantum-mechanical principles. Its significance lies not only in the fact that carcinogenic potency (or otherwise) has been correctly predicted on purely theoretical grounds for quite a large number of molecules which had not, at that time, been investigated experimentally; but also in the fact that it opens up new fields of enquiry and discovery, and itself suggests new interpretations: this must inevitably lead to a better understanding of such phenomena as cocarcinogenesis, anticarcinogenesis, drug action, chemical mutations, and the mechanism of estrogenic and other hormone activity. There is little doubt but that in the next two or three decades we may expect enormous and far-reaching developments in these fields; and the developments are likely to be considerably facilitated if there is a fairly large body of experimenters who are familiar with the quantum-mechanical basis on which, quite evidently, the action of these chemicals must ultimately depend. It is for this reason that (2) and (3) have been

written in their present form. Those who are already familiar with wave-mechanical methods can pass straight to the remaining sections of this review.

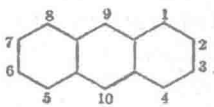
II. Historical Survey

1. The K-Region

It was established about twenty years ago that certain polycyclic hydrocarbons have the property of inducing cancerous growths, either when painted on the skin or injected into the animal concerned. Nearly

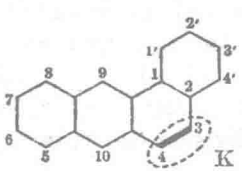


Phenanthrene
(I)

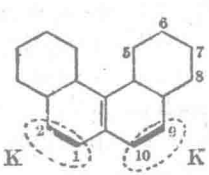


Anthracene
(II)

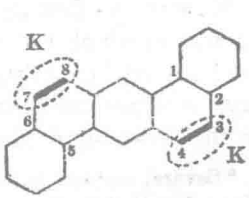
all these molecules could be regarded as derivatives of phenanthrene (I), though phenanthrene itself is not active. The staggered ring system of phenanthrene seems to be much more effective in promoting carcinogenic activity than does the straight type of annelation shown in anthracene (II), derivatives of which are hardly ever active. (An exception is 9,10-dimethylanthracene, which is the simplest known carcinogen among the hydrocarbon family. No satisfactory explanation of this has yet been suggested.) It is customary now to distinguish between the anthracene —and phenanthrene—type skeletons by saying that in the latter the 9,10-region has a character quite distinct from anything in the former. Following Mme. Pullman (1946c, 1947c) we shall call this the K-region. The K-region is easily recognized. Thus in the extremely important parent hydrocarbon 1,2-benzanthracene (III) there is one K-region, as shown by a thick line: in 3,4-benzphenanthrene (IV) and 1,2,5,6-dibenzanthracene (V) there are two K-regions. Our study of these molecules will largely consist of an enquiry concerning the electronic distribution in these regions and of the ways in which this distribution is affected by



1,2-Benzanthracene
(III)

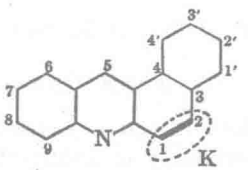


3,4-Benzphenanthrene
(IV)



1,2,5,6-Dibenzanthracene
(V)

substitution (particularly methyl substitution), or by an aza replacement such as occurs when benzanthracene (III) is compared with benzacridine (VI).



3,4-Benzacridine*
(VI)

At this stage reference must be made to the exceedingly valuable compilation of Hartwell (1941), who has listed all the available published (and unpublished) experimental results with molecules of the kind we are interested in. Practically all the experimental conclusions mentioned in this review are quoted from Hartwell's quite invaluable tables. To this, and to the review article by Badger (1948) the writer is greatly indebted.

2. Schmidt's Box Model

The first attempt to explain the significance of the K-region was due to Schmidt (1938, 1939a,b,c, 1941). In essence this amounted chiefly to an explanation, largely in classical terms (Schmidt's wave-mechanical considerations were somewhat speculative, and have never gained general acceptance), to show why this region might be expected to behave differently from any other region in an aromatic system. Schmidt started with the hypothesis that there were certain regions, or groupings, of peculiar stability, which would try to preserve their character in any chemical reaction, so far as that was possible. Such groupings include benzene and naphthalene, but they do not include open-chain structures such as butadiene. The complete molecule can then be cut up into separate units as in Fig. 1, which suggests that phenanthrene and benzanthracene (a) should exhibit peculiarly strong reactivity precisely in their K-regions, but anthracene (a) should not. Rather is it that the reactivity of anthracene should reside in the meso, or 9,10-positions.

Now in the first and third of these molecules there is no doubt about the way in which the "boxes" should be drawn. Any attempts, such as those shown for anthracene (b), (c) to cut up the molecule in any other way, involves using an open-chain unit such as butadiene or ethylene. On the other hand, the rules do not prohibit the division shown in benz-

* Several distinct numbering systems are in use for this and other related molecules. For that reason we shall usually place our numbering scheme on the diagrams of the molecules in the text where they first occur.

anthracene (b), and we are left wondering whether there is, or is not, a special K-region in this molecule.

It is certainly true that the units (or boxes) chosen by Schmidt are very stable ones, when they occur alone. Thus benzene has a resonance energy of 38 kcal./mole, and naphthalene nearly twice as much, compared with about 6 to 8 kcal./mole for butadiene. But there is no direct correlation between the behavior of the units when they occur as distinct molecules and when they occur as parts of a larger system. The evidence from ultraviolet absorption spectra suggests that molecules of this kind behave as single systems, whereas on Schmidt's view we might have expected each component unit to absorb separately from the rest. The

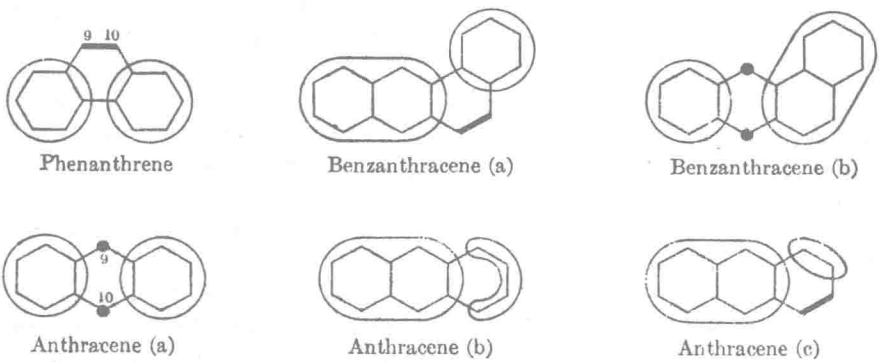


FIG. 1. The "Box Model" of Schmidt.

theoretical basis for this theory is therefore destroyed, and, in view of the uncertainty about drawing the boxes and the almost complete lack of quantitative deduction that can be drawn from it, we can regard the theory merely as suggestive. It suggests (a) that the possession of a phenanthrene-type region is likely to make the behavior of a molecule different from that of molecules without this region, (b) that the K-region bond would be expected to be the seat of the enhanced reactivity, and (c) that in cases where no unique division into boxes is possible, there may be a double type of reactivity. This would mean that in benzanthracene, for example, both the K-region 3,4- and also the meso-positions 9,10 would have characteristic and important properties.

We shall see later that all these suggestions correspond to the truth. In particular phenanthrene does differ from most aromatics in adding hydrogen at the 9,10-positions (we shall discuss the so-called osmium tetroxide reaction later), and this addition is much easier than in benzene. Also the meso-positions in anthracene, and in benzanthracene too, are outstandingly important, both chemically (anthracene forms a photo-

oxide in which —O—O— links these two atoms) and carcinogenically (substituents at these positions tend to be more effective than at other places in the skeleton).

3. *Svartholm's Introduction of π Electrons*

Schmidt's work was unsatisfactory because it did not do justice to our knowledge of the electronic structure of molecules. The next step—and in some ways the most significant—was due to Svartholm (1941), though he does not appear to have fully appreciated the significance of his work. We shall not now describe in detail the analysis that he gave, because it has subsequently been developed much more fully by Mme. Pullman and R. Daudel, and will form the substance of Sec. III. But, in essence, Svartholm accepted the description of an aromatic molecule in the form in which it had been given by Pauling and his co-workers. This treated the molecule as if it could be described as a simultaneous superposition of several so-called structures. These structures were nothing other than ways of drawing the necessary number of single and double bonds, as in the Kekulé and Dewar structures of benzene. Wave mechanics showed that in the superposition some of these structures were more important than others, and thus that certain bonds were more nearly double bonds than were the others. Pauling, Brockway, and Beach (1935) had already used the concept of fractional bond order, which was implicit in Svartholm's work. Svartholm showed that in phenanthrene and similar molecules the K-region did resemble a double bond much more closely than did any other bond. From this he concluded that this region could more easily add other groups or attach itself to the cell than could other regions. It was not unreasonable, therefore, to regard it as the seat of carcinogenic activity. A second conclusion followed, though it was less clearly stated. In anthracene and other similar molecules there appeared to be a considerable unused bonding power at the meso-positions 9,10. These atoms would be expected also to be reactive for addition, so that, in cases such as benzanthracene where there was both a K-region and a pair of meso-atoms, we might expect one to be able to influence the other.

The significant advance made by this work can be summarized: (a) it made use of a quantum-mechanical description of molecular structure; (b) it showed that there really were certain special electrical properties associated with the K-region, and that these were capable of being calculated theoretically; finally (c) it threw emphasis on to the behavior of the electrons responsible for conferring double-bond character on the bonds of an aromatic molecule. These are the π electrons, which we shall describe more fully in Sec. III. All this carried the problem into

the region of molecular structure, where, at this time, considerable advances both of a fundamental and a technical kind, were being made.

4. The Work of Pullman, Daudel and Others

The next stage, which includes much the greater part of the work which we are reviewing, is due to the French school of theoretical chemists, Dr. and Mrs. Daudel, Dr. and Mrs. Pullman, and their colleagues. There has been a good deal of double publication, so that it is not easy always to be sure of the priorities. But the first full-scale report of the application to carcinogenic problems is given by Mme. Pullman (1945a,b, 1946a,c, 1947c). This includes the effects of aza substitution in the carbon skeleton and of methyl substitution around the periphery of the molecule. In order to develop this theory, however, it was necessary first to investigate the numbers of structures (in the sense used by Slater and Pauling—see Sec. III) of given type; and in this work R. Daudel and Mme. Pullman largely published together (A. Pullman, 1946b; B. Pullman, 1946; Daudel, 1946a; Daudel and Pullman, 1945b,c,d,e, 1946). More recently a review of some aspects of this problem has been given by Daudel and Daudel (1950), and a semihistorical account of much of the earlier work has been provided by R. Daudel (1946b). Very recently also a list of molecules for which carcinogenic potency has been predicted on theoretical grounds has been given by Daudel and Daudel and Buu-Hoi (1950).

These workers effectively took Svartholm's model, and made it quantitative. This involved, on the one hand, a very laborious solution of a large number of sets of simultaneous equations, and on the other hand, an estimate of the way in which the greater electronegativity of a nitrogen atom as compared with a carbon attracted electrons away from the K-region on to the nitrogen: and in which the electron-donating character of a methyl group replenished the supply of electrons in this region. Running through all this work was the conviction that some threshold existed for this region, and if what we may describe as the "electrical index" of this region exceeded the threshold value, the molecule would be carcinogenic: otherwise it would not be. The precise nature of what constitutes this electrical index is one of the major problems to be solved. Even now our judgment about it is continually changing as further experimental evidence accumulates. In Svartholm's early work it was supposed that the bond order provided the effective index; in Pullman's work on unsubstituted hydrocarbons it was the sum of bond order in the K-region and the two free valences at the carbons of this region; in substituted hydrocarbons and aza molecules it was the so-called total charge of this region (this is essentially the sum of bond order, free valences, and