have been discussed by Cameron (*32*), Johnson (*33*), Manley (*34*), and Matsuoka *et al.* (*35*).

On the basis of the rather crude x-ray positional data that were available in the fall of 1966, Sandage made a photographic survey of a 4- by 4-degree region surrounding Cyg XR-2. Subsequently, more accurate information was provided by the ASE–MIT group, which led to an identification of Cyg XR-2 with a 16th-magnitude blue star noted on the Palomar plates. If the identification is confirmed, Cyg XR-2 and Sco XR-1 will be "charter members" of a newly recognized class of stars, located in our own galaxy, whose x-ray luminosities considerably exceed their optical outputs.

References and Notes

1. The 1967 Texas Symposium had a registration of approximately 650 persons. The organizing committee and sponsoring organizations consisted of A. G. W. Cameron, Belfer Graduate School of Science, Yeshiva University, and NASA Goddard Institute for Space Studies; Ivor Robinson, Southwest Center for Advanced Studies; and E. L. Schucking and Alfred Schild, University of Texas. The symposium was cosponsored by the American Physical Society and the American Astronomical Society and was supported by the Office of Naval Research, the National Science Foundation, the U.S. Atomic Energy Commission, the National Aeronautics and Space Administration, the Carnegie Institution of Washington, and the General Electric Space Sciences Laboratory.
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55. We are grateful to Drs. Thaddeus, Simpson, and Friedman for permission to reproduce the figures accompanying this article, to Dr. Dent for helpful suggestions, and to Miss K. I. Moyd for providing a translation of the paper that Professor Shklovskii presented at the symposium. This article is Kitt Peak National Observatory contribution No. 262.

Hydroxylation-Induced Migration: The NIH Shift

Recent experiments reveal an unexpected and general result of enzymatic hydroxylation of aromatic compounds.

Gordon Guroff, John W. Daly, Donald M. Jerina, Jean Renson, Bernhard Witkop, Sidney Udenfriend

In 1955, Mason and his collaborators discovered that the enzymatic oxidation of 3,4-dimethylphenol to 4,5-dimethylcatechol led to the incorporation of oxygen from molecular oxygen but not from water (*1*). This observation was in sharp contrast to the concept of biological oxidation held at that time, and it paved the way for the investigation of an important class of enzymes now known to introduce atmospheric oxygen into a large and diverse group of substrates. These oxygenase enzymes, the subject of several recent review volumes (*2*), function in a bewildering variety of metabolic processes and differ substantially in many aspects of their action. The use of O^{18}, a heavy isotope of oxygen, has greatly increased current knowledge of the mechanism of action of oxygenases, including the large and important subgroup known as hydroxylases or "mixed function oxygenases."

Recent studies in our laboratories with aromatic substrates labeled in specific positions with deuterium or tritium have uncovered what appears to be a fundamental property of aromatic hydroxylation reactions. These experiments indicate that a frequent conse-

quence of hydroxylation is an intramolecular migration or shift of the group displaced by hydroxyl to an adjacent position on the aromatic ring. This is in contrast to the classical concept of aromatic substitution in which the group at the site of substitution would be lost by direct replacement. These investigations have yielded many interesting and surprising results and encouraged predictions and interpretation of both enzymatic and nonenzymatic reactions in terms of organic chemical mechanisms. Furthermore, awareness of this phenomenon has made possible the development of enzymatic assay methods that were not available in the past. In order to simplify further discussion, the phenomenon of hydroxylation-induced intramolecular migration has been given the name "NIH Shift."

Before the phenomenon and its significance were recognized a number of puzzling and frustrating observations were made during enzymatic hydroxylation of tritiated aromatic substrates. For example, several years ago an investigation into the mechanism of action of the aryl hydroxylase of liver microsomes occasioned the synthesis of 4-tritioacetanilide (acetanilide-4-^{3}H). The purpose was to devise a simple, rapid assay for the aryl hydroxylase based on displacement of the tritium as shown in Fig. 1. Hydroxylation of this material occurred and could be demonstrated colorimetrically, but the startling observation was made that only a small and variable fraction of the expected amount of tritiated water was released. In addition, the product, 4-hydroxyacetanilide, contained large amounts of radioactivity. At that time these results were interpreted to mean that the substrate, acetanilide, was labeled in positions other than the 4-position and, after several apparently unsuccessful attempts to prepare acetanilide specifically labeled in the 4-position, the studies were discontinued.

More recently, another attempt was made to develop an assay for a hydroxylase, based on the use of a specifically tritiated substrate. The enzyme, tryptophan-5-hydroxylase, which catalyzes the initial step in the biosynthetic pathway to serotonin, had resisted study partly because of the lack of a simple and sensitive assay. Accordingly, 5-tritiotryptophan was synthesized and used as a substrate for partially purified preparations of tryptophan-5-hydroxylase. Again, as in the case of the microsomal hydroxylation of 4-tritioacetanilide, substantial hydroxylation could be shown to occur, but little tritium was released from the substrate. Although these data could be explained by a massive isotope effect, the observation that the 5-hydroxytryptophan which was formed contained large amounts of tritium made this explanation untenable. Once again doubt was raised that the substrate was, in fact, specifically labeled in the 5-position.

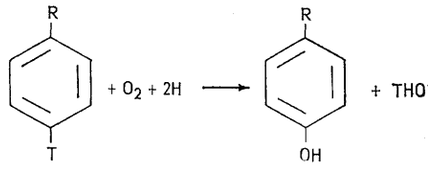

Fig. 1. Expected replacement of tritium by hydroxyl.

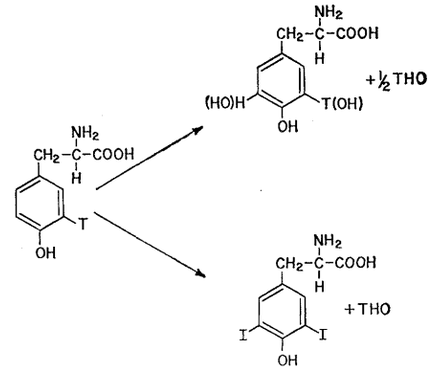

Fig. 2. Proof of the structure of the tritiotyrosine formed from 4-tritiophenylalanine by phenylalanine hydroxylase.

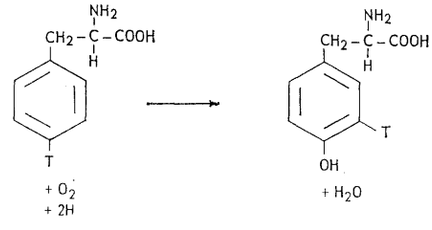

Fig. 3. Action of phenylalanine hydroxylase on 4-tritiophenylalanine.

At the same time, in the course of experiments with several phenylalanine-hydroxylating enzymes, an attempt was made to utilize 4-tritiophenylalanine to measure phenylalanine hydroxylation. In this case also, little tritium was released, and the tyrosine which was formed contained almost as much radioactivity as the substrate, phenylalanine.

At this point, the available information indicated that in three hydroxylation reactions, presumably specifically labeled aromatic substrates were being converted to phenolic products which retained substantial amounts of the tritium which was originally present at the site of the entering hydroxyl group. The possible explanations seemed limited to either nonspecific or incorrect labeling of the substrates, or migration of the displaced group. Unequivocal localization of the isotope in the substrates became the crucial point of the investigation. Since, in a tritiated compound, only trace amounts of hydrogen are replaced by tritium, the position of the isotope is difficult to determine conclusively. Deuterium, on the other hand, can be used to replace specific hydrogens completely. Therefore an appropriately deuterated substrate was synthesized, and the position of the isotope on the aromatic ring was unequivocally determined by nuclear magnetic resonance spectroscopy.

Enzymatic Hydroxylation

Phenylalanine hydroxylase. Deuterophenylalanine was prepared by the reductive deuteration of 4-bromo-DL-phenylalanine. The deuterated product was degraded to benzoic acid and examined by nuclear magnetic resonance spectroscopy. The spectrum (A_2B_2 pattern) proved that the deuterium was located exclusively in the 4-position. The mass spectrum of the deuterated amino acid showed that the material contained only one deuterium per molecule. The 4-deuterophenylalanine was then used as a substrate for bacterial phenylalanine hydroxylase, and the tyrosine produced was isolated. Sixty to seventy percent of the deuterium of the substrate was retained in the product (*3*). This experiment provided the first unequivocal demonstration of hydroxylation-induced migration in these studies.

Information as to the new location of the substituent originally in position-4 was obtained by studies with tritiated phenylalanine (*4*). This material, tritiated by the same procedure used to prepare the deuterated compound, was treated with bacterial or with liver phenylalanine hydroxylase. In each case the resulting tyrosine contained almost as much tritium as the original 4-tritiophenylalanine. A portion of the tyro-

Drs. Guroff and Renson are members and Dr. Udenfriend is chief of the Laboratory of Clinical Biochemistry, National Heart Institute; Drs. Daly and Jerina are members and Dr. Witkop is chief of the Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland.

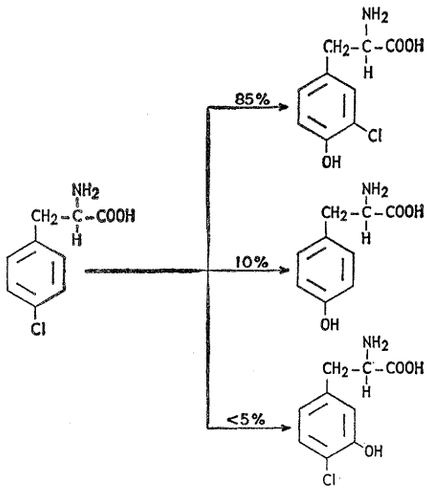

Fig. 4. Action of phenylalanine hydroxylase on 4-chlorophenylalanine.

sine formed from 4-tritiophenylalanine, upon oxidation with tyrosine hydroxylase to give 3,4-dihydroxyphenylalanine released half of its tritium as tritiated water. Another portion was treated with *N*-iodosuccinimide to give 3,5-diiodotyrosine. All the tritium of the tyrosine was replaced by the halogen (Fig. 2). These findings showed that the tritium which was originally in the 4-position of phenylalanine had migrated to the 3-position of tyrosine adjacent to the hydroxyl group (Fig. 3).

Further studies were carried out to determine the fate of the hydrogen in the 3-position of phenylalanine; that is, the one originally present in the position to which in the 4-position tritium had migrated. Accordingly, experiments were carried out with 3,5-ditritiophenyalanine (*5*). The 4-hydroxylation of this material with phenylalanine hydroxylase produced tyrosine with almost the same specific activity as the substrate, there being little or no loss of tritium during the hydroxylation. This finding provided crucial information concerning the mechanism of the migration, as will be discussed later.

Chlorine and bromine substituents also undergo hydroxylation-induced migration (*6*, *7*). The action of phenylalanine hydroxylase on 4-chlorophenylalanine leads to the formation of three products (Fig. 4). The formation of 3-chlorotyrosine shows the halogen migration. The appearance of 3-hydroxy-4-chlorophenylalanine suggests that hydroxyl migration can also occur. Comparable migrations were observed with 4-bromophenylalanine. In contrast, 4-fluorophenylalanine was oxidized to tyrosine with complete loss of fluorine.

We now have some indication that the hydroxylation of 4-methylphenylalanine leads to a migration of the methyl group (*8*).

Tryptophan-5-hydroxylase. Concurrent investigations with a tryptophan-hydroxylating enzyme from mouse mast cells have shown that an analogous migration occurs during the hydroxylation of 5-tritiotryptophan (*9*). At least 85 percent of the tritium was retained. The product had the same tritium lability as authentic 4-tritio-5-hydroxytryptophan (*10*), proving that the migration of tritium had proceeded selectively to the 4-position (Fig. 5). Similar observations have been made with the tryptophan hydroxylase system of *Chromobacterium violaceum*. The further observation that 4-tritiotryptophan lost essentially no tritium upon 5-hydroxylation is consistent with the data obtained upon hydroxylation of 3,5-ditritiophenylalanine with phenylalanine hydroxylase.

Aryl hydroxylase of rabbit liver microsomes. Migration of deuterium and tritium from the 4-position of acetanilide to one of the equivalent neighboring positions of 4-hydroxyacetanilide (Fig. 6) has been demonstrated (*11*). The retention of deuterium and tritium in the hydroxylated products were 15 and 45 percent, respectively. The remainder of the tritium appeared as tritiated water. The amount of tritium retained in the product varied with the *p*H of the incubation medium, the retention increasing as the *p*H was lowered. The retention was 67 percent at

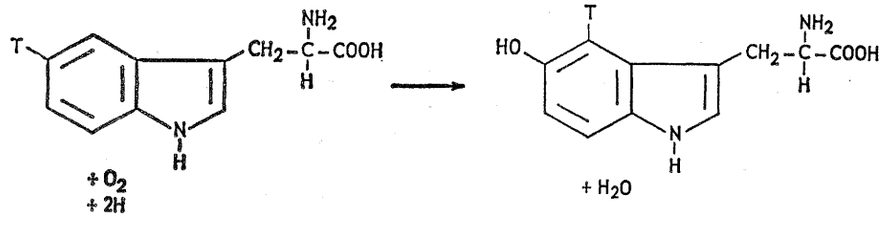

Fig. 5. Action of tryptophan-5-hydroxylase on 5-tritiotryptophan.

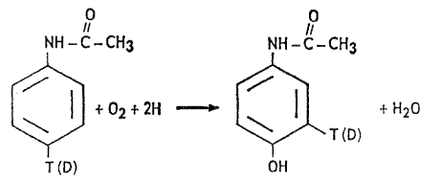

Fig. 6. Action of liver microsomal hydroxylase on 4-tritioacetanilide.

*p*H 6.2 and 37 percent at *p*H 9.0. The extent of retention of tritium was virtually the same whether rabbit or rat liver microsomes were used (*12*).

Experiments with the liver microsomal system have proved conclusively that the migration is intimately associated with the hydroxylation process. Migration did not precede hydroxylation since, when the remaining 4-tritioacetanilide substrate was reisolated from an incubation mixture, the tritium was still in the 4-position. That this was the case was determined by either chemical hydroxylation or bromination of the reisolated substrate. The 4-hydroxy- or 4-bromoacetanilide produced contained no tritium. Furthermore, the residual substrate retained its original specific activity, an indication that no exchange was catalyzed by the enzyme independent of hydroxylation. Experiments with 3,5-ditritioacetanilide demonstrated that no tritium was lost from the molecule upon 4-hydroxylation. These results are consistent with those obtained with 3,5-ditritiophenylalanine and with 4-tritiotryptophan.

The nonspecificity of the microsomal enzyme permitted us to study the retentions of tritium in various substrates (*12*). The microsomal hydroxylation of 4-tritioamphetamine led to a retention of 90 percent. On the other hand, the hydroxylation of 5-tritiosalicylic acid to gentisic acid and of *N*-acetyl-3,5-ditritiotyramine did not lead to significant retention of tritium. These data, together with the acetanilide data and the experiments on the other enzymes, give substance to a theory about the mechanism of the migration which is presented later.

Experiments with intact rats proved that tritium migrations occur in vivo as well as in vitro. Administration of 4-tritioamphetamine and 4-tritioacetanilide led to the excretion of the glucuronides of the 4-hydroxylated products, 4-hydroxyamphetamine and 4-hydroxyacetanilide, containing 90 and 38 percent, respectively, of the specific activity of the administered materials.

Tyrosine hydroxylase. The hydroxylation of 3,5-ditritiotyrosine by tyrosine hydroxylase leads to 3,4-dihydroxyphenylalanine with the stoichiometric release of one tritium atom as tritiated water, providing a convenient assay for the enzyme (*13*). This is comparable to the hydroxylation of *N*-acetyl-3,5-ditritiotyramine by the microsomal enzyme. By contrast, the hydroxylation of 4-tritiophenylalanine with this enzyme (*14*), as with liver and bacterial phenylalanine hydroxylase, yielded tyrosine in which tritium was retained (*15*).

4-Hydroxyphenylpyruvic acid oxidase. The conversion of 4-hydroxyphenylpyruvic acid to homogentisic acid has until now been considered a unique reaction. However, the analogy with the preceding migrations is apparent. In this case, an alkyl side chain migrates as a result of hydroxylation (*16*). Similar migrations of the alkyl side chain are observed upon hydroxylation of phenylpyruvic acid and *p*-fluorophenylpyruvic acid (*17*).

Applications to enzyme assay. A recognition and understanding of the tritium migration has made it possible to devise simple and sensitive isotope assays for some of these hydroxylases. With tritiophenylalanine as substrate, a method for the determination of phenylalanine hydroxylases has been developed, which depends upon the iodination of the tritiotyrosine produced to displace the isotope from the 3-position (*18*). By appropriate modification, this method has also been applied to the measurement of the reduced pteridines which serve as hydroxylase cofactors in biological materials (*19*). An even simpler procedure can be devised to measure the activity of tryptophan-5-hydroxylase based on the acid lability of the tritium in the 4-position of 5-hydroxytryptophan (*20*). Assays of this type can be used to measure the microsomal enzyme and presumably other enzymes whose actions involve tritium migration.

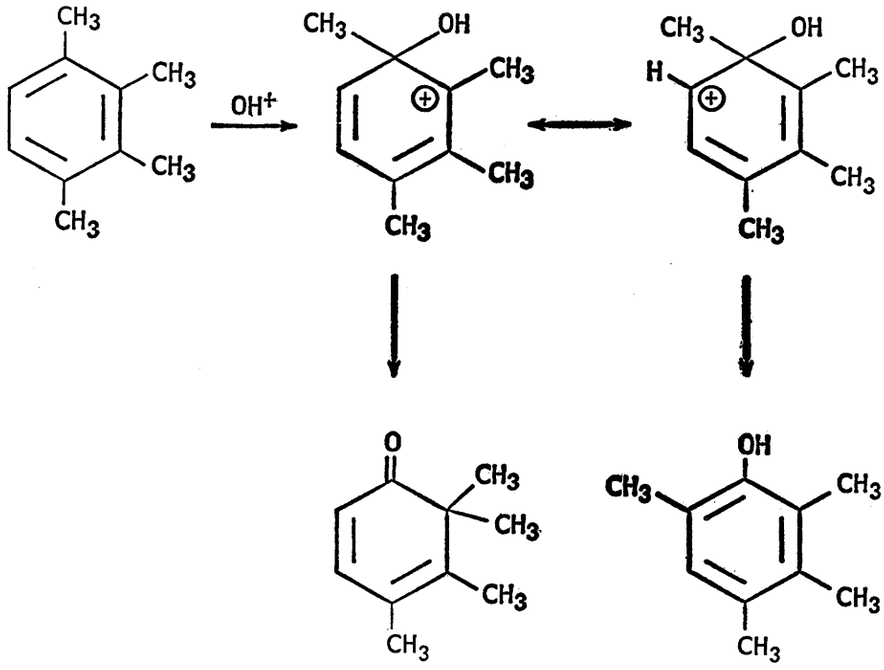

Fig. 7. Action of trifluoroperacetic acid plus boron trifluoride on prehnitene.

Nonenzymatic Substitution Reactions of Aromatic Compounds

The possible occurrence of such migrations during nonenzymatic substitutions were now investigated. The well-known electrophilic substitution reactions—bromination, nitration, diazonium coupling, and Friedel-Crafts acylation and alkylation—of various specifically labeled aromatic compounds were examined. No migration of tritium or deuterium was observed (*21*). This is in accord with previous isotopic studies (*22*).

Migration of halogen substituents in the presence of aluminum halide catalysts at elevated temperatures has been reported (*23*). Both chlorine and bromine migrate under these conditions, whereas fluorine does not. These observations are in accord with the migration of chlorine and bromine and the loss of fluorine on enzymatic hydroxylation (*6, 24*).

Nonenzymatic hydroxylation. Mechanistic considerations prompted us to study either electrophilic substitutions exhibiting a large primary isotope effect, such as mercuration (*25*) and sulfonation (*26*), or electrophilic reagents containing an unshared pair of electrons that would be available for the stabilization of the charge in the transition state. These electrophilic reagents involve species such as HO^+ and CH_3O^+. For example, 4-substituted phenols on oxidation with Caro's reagent (*27*), which is a source of HO^+, or with lead tetraacetate (*28*) give rise to hydroquinones substituted in the 2-position, whereas oxidation of prehnitene (1,2,3,4-tetramethylbenzene) with trifluoroperacetic acid, another source of HO^+, in the presence of boron trifluoride (*29*) leads to migra-

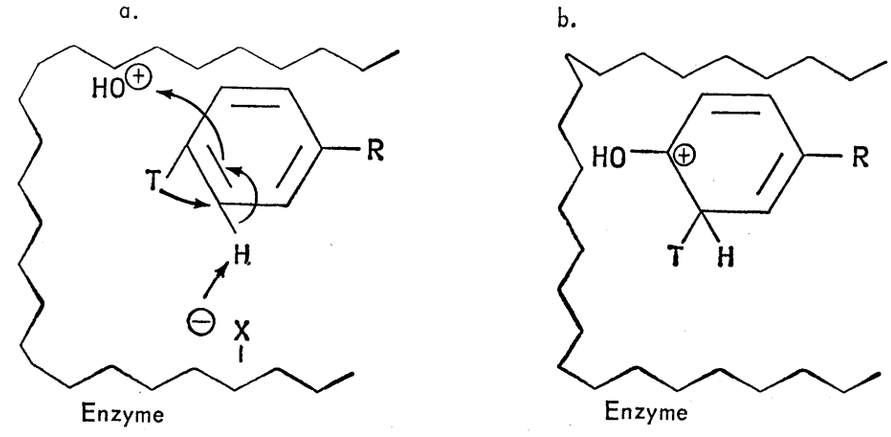

Fig. 8. Possible mechanisms for hydroxylation-induced intramolecular migration.

tion of alkyl substituents (Fig. 7). Recent investigations (*21*) have shown that analogous migrations of tritium and deuterium do occur during hydroxylation of 4-tritio- and 4-deuteroacetanilide with trifluoroperacetic acid. The retention of tritium in the product, 4-hydroxyacetanilide, was only 10 percent compared to the retention of 40 to 65 percent obtained upon microsomal hydroxylation.

Hydroxylation of 4-tritioacetanilide by other hydroxylating systems previously favored as models for enzymatic hydroxylation, showed no signficant retention. These systems included the Hamilton system (*30*) which consists of hydrogen peroxide and catalytic amounts of catechol and ferrous ion; the Fenton system which consists of hydrogen peroxide, ethylenediaminetetraacetic acid, and ferrous ions (*31*); and the Udenfriend system which consists of ascorbic acid, ferrous ion, and O^2 (*32*).

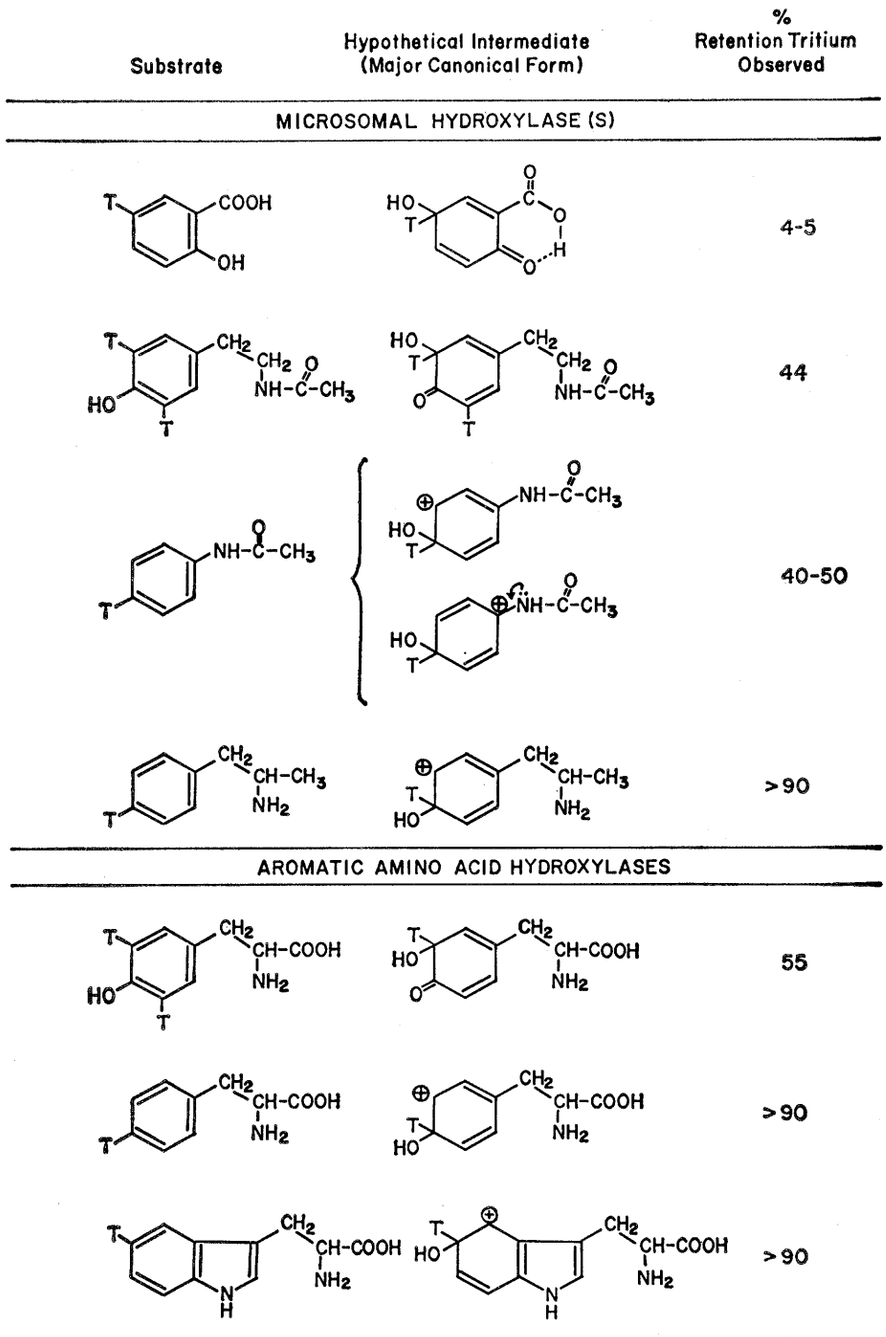

Fig. 9. Action of microsomal hydroxylase on various substrates; correlation of probable charge distribution of intermediates with observed tritium migration.

Possible Mechanisms of Reaction

The "NIH Shift" occurs with a sufficiently large number of enzymes and substrates (Table 1) that one may consider it to be a general phenomenon of aromatic hydroxylation. The key question in our studies concerns the mechanism of the migration. One possibility is a "concerted" mechanism analogous to many other substitutions, displacements, and migrations. By this mechanism the enzyme would deliver the hydroxylating species, derived from a molecule of enzyme-bound oxygen, concomitant with removal of the neighboring hydrogen and migration of tritium (Fig. 8a). In this mechanism the enzyme would be an obligatory participant in the migration. The experiments with 3,5-ditritiophenylalanine, 4-tritiotryptophan, and 3,5-ditritioacetanilide provide convincing evidence against such a concerted attack, since no radioactivity was lost from the adjacent position or positions during the hydroxylation.

A "stepwise" mechanism consistent with the data is pictured in Fig. 8b. In this mechanism the enzyme would play no role beyond the addition of hydroxyl to a specific position on the molecule. The formulation of cationic cyclohexadiene intermediates is, of course, hypothetical. The important feature is that a disubstituted intermediate with tritium and hydrogen in the 3-position would be formed whether tritium is displaced from the 4-position by hydroxyl or is in the 3-position originally. The degree of retention of tritium in the molecule on rearomatization would depend upon the strength of the carbon-tritrium bond relative to that of the carbon-hydrogen bond.

If a stepwise mechanism leading to a charged intermediate is, in fact, responsible for the migration, then the charge distribution in the hydroxyl-substituted intermediate should determine the extent to which migration occurs. Studies with various substrates and the microsomal enzyme provided evidence that this is, in fact, the case (*12*). It was shown (Fig. 9) that the amount of tritium retained through migration correlated well with probable charge distribution patterns in the hydroxyl-containing intermediates.

The 5-hydroxylation of 5-tritiosalicylic acid leads to a *para*-quinoid intermediate (Fig. 9) in which the loss of tritium would be favored over migra-

Table 1. Hydroxylations in which migration has been demonstrated.

Substrate	Enzyme	Major product
4-Deuterophenylalanine	*Pseudomonas* phenylalanine hydroxylase	3-Deuterotyrosine
4-Tritiophenylalanine	Liver phenylalanine hydroxylase	3-Tritiotyrosine
4-Tritiophenylalanine	*Pseudomonas* phenylalanine hydroxylase	3-Tritiotyrosine
4-Tritiophenylalanine	Adrenal tyrosine hydroxylase	3-Tritiotyrosine
4-Chlorophenylalanine	Liver phenylalanine hydroxylase	3-Chlorotyrosine
4-Chlorophenylalanine	*Pseudomonas* phenylalanine hydroxylase	3-Chlorotyrosine
4-Bromophenylalanine	Liver phenylalanine hydroxylase	3-Bromotyrosine
4-Bromophenylalanine	*Pseudomonas* phenylalanine hydroxylase	3-Bromotyrosine
5-Tritiotryptophan	Mast cell tryptophan hydroxylase	4-Tritio-5-hydroxytryptophan
5-Tritiotryptophan	*Chromobacterium violaceum* tryptophan hydroxylase	4-Tritio-5-hydroxytryptophan
4-Deuteroacetanilide	Liver microsomal aryl hydroxylase	3-Deutero-4-hydroxyacetanilide
4-Tritioacetanilide	Liver microsomal aryl hydroxylase	3-Tritio-4-hydroxyacetanilide
4-Tritioamphetamine	Liver microsomal aryl hydroxylase	3-Tritio-4-hydroxyamphetamine
4-Hydroxyphenylpyruvic acid (*16*)	*p*-Hydroxyphenylpyruvate hydroxylase	Homogentisic acid
Phenylpyruvic acid (*17*)	*p*-Hydroxyphenylpyruvate hydroxylase	2-Hydroxy-5-fluorophenylacetic acid
4-Fluorophenylpyruvic (*17*)	*p*-Hydroxyphenylpyruvate hydroxylase	2-Hydroxy-5-fluorophenylacetic acid

tion and retention. The same principle is involved in the 3-hydroxylation of *N*-acetyl-3,5-ditritiotyramine by liver microsomes and of 3,5-ditritiotyrosine by tyrosine hydroxylase. In both cases one of the tritium atoms is lost from the *ortho*-quinoid intermediate.

In the hydroxylation of 4-tritioacetanilide the positive charge in the transition state is stabilized by resonance structures to which the electron pair at the nitrogen contributes (Fig. 9). This contribution not only stabilizes but also delocalizes the positive charge for this substrate. It is therefore not surprising that the migration of tritium for this substrate is less than in the following examples.

Both the hydroxylation of 4-tritioamphetamine (microsomal hydroxylase) and of 4-tritiophenylalanine (phenylalanine hydroxylase) should lead to transition states in which the positive charge is present mainly in either of the adjacent positions. The high retention observed with these substrates is therefore predictable.

The hydroxylation of 5-tritiotryptophan leads to transition states in which the positive charge is better stabilized in the 4- than in the 6-position. The experiment confirmed the prediction that essentially all the tritium retained in the product would reside in the 4-position.

The emergence of such a consistent chemical picture makes it likely that the "NIH Shift" is a function of the structure of the hydroxyl-substituted intermediate rather than a direct consequence of the mechanism of enzyme action. From this point of view the reaction can be discussed in two parts: (i) enzymatic hydroxylation of suitable substrates leading to cationoid transition states and (ii) formation of one or more products from these intermediates. At the present time, it appears that the second step may not be enzyme-mediated at all.

This, however, raises the further question of why enzyme-catalyzed reactions show much greater retentions with the same substrates than the chemical hydroxylations do. The reason for this and the relations between enzymatic and nonenzymatic hydroxylations are important questions.

The numerous possibilities for loss or migration of substituents during en-

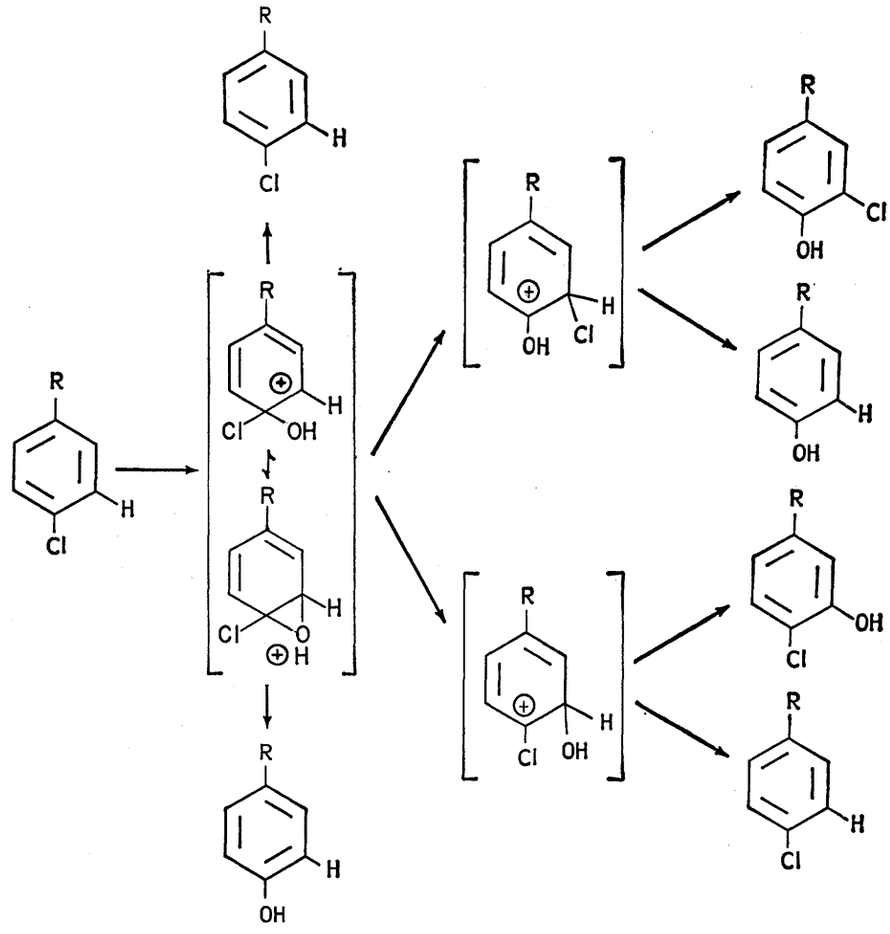

Fig. 10. Products of and postulated intermediates in the action of phenylalanine hydroxylase on 4-chlorophenylalanine.

zymatic hydroxylation are shown in Fig. 10 for the representative case of 4-chlorophenylalanine. The ratio of products is probably determined not only by the point of initial hydroxyl attack but also by the several kinetic factors in each of the possible reactions. The example explains how one enzyme can produce several products from a single substrate. This is of particular significance in drug metabolism, where a single enzyme could account for a great number of urinary products. The diagram also shows that it is possible to have a substitution occur and yet observe no net reaction ("virtual reaction"). The recognition of the "NIH Shift" has shown that hydroxyl group substitution is not limited to positions *ortho*, *meta*, and *para* to a ring substituent but frequently occurs on the same carbon atom as the substituent itself. Finally, the possibility of the reaction of the cationoid intermediates with external nucleophiles could give rise to products such as dihydrodiols (*33*) or mercapturic acids (*34*). Thus, the discovery of the "NIH Shift" has provided new insights into the mechanism of hydroxylation and allowed the development of new tools for enzyme assay. In addition, the findings have opened fascinating new possibilities for metabolic pathways and led to exciting experiments on the relationship of chemical models to enzymatic processes.

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Graduate Student Stipends

Greater reliance on the "traineeship" concept would facilitate a more purposeful and consistent treatment.

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Human institutions, as all of us know, generally outlive the circumstances which motivated their establishment. Arrangements adopted by the federal government for support of university science are no exception, and this article discusses one case in point. Considerations which originally gave rise to various forms of graduate student support are reviewed and some are found to have diminished in relevance. Currently prevalent attitudes appear to be best reflected in the traineeship approach.

The discussion here deals with students of physics. Conditions of employment, as well as the reasons for these conditions, differ somewhat from one scientific discipline to another. One purpose of this article is to elicit some public discussion of the differences and how they bear upon policies of student support.

The classical form of graduate student support (private fellowships, teaching assistantships, and outside employment) all persist at a significant level in our system today. To these have been added a great diversity of stipends provided by the federal government. Such stipends include: National Science Foundation predoctoral and cooperative fellowships, Atomic Energy Commission fellowships, National Science Foundation traineeships, National Defense Education Act fellowships, research assistantships under research grant and contracts awarded by numerous federal agencies, stipends provided under "University Science Development" grants, and doubtless several others. Each mode of support has its own nominating or selecting procedures and its own reporting or supervisory requirements. These multifarious arrangements impose a burden upon university faculties, federal administrators, and the students themselves. Confusion prevails, and we are learning

The author is head of the physics section of the National Science Foundation. This article is based on portions of a seminar given at the University of Washington in May 1965 and is offered not as a pronouncement but rather as an interesting starting point for community discussion. Opinions or assertions are the private ones of the author, and are not to be construed as official or as representing the views of the National Science Foundation.