the solvent, $(\partial\rho_N/\partial c_2)_\mu$ is the scattering length density increment, and b_2 and b_i are scattering lengths per gram of component. These quantities are defined by the known chemical compositions of the components. Equations 1 and 3 can now be solved for $\bar{v}_2$ and ξ_i for identical solvent components without further assumptions. Good results were achieved by the combination of mass and neutron data of halophilic enzymes[82] because b_1 is very different from b_2 or b_3; in fact, it is of opposite sign. We have now applied[42] these considerations to recent neutron scattering data of Lederer et al.[83] on a 130-bp NaDNA fragment of known sequence, containing the strong promoter A1 of the *E. coli* phage T7, and calculate $\bar{v}_2 = 0.503$ in 0.1 M NaCl, in good agreement with well-proven mass measurements, which are rather difficult to perform at high concentrations of salt (Figure 2).

Concluding Remarks

In this work I have summarized structural and biophysical studies on DNA since the discovery of the double helix in 1953, stressing aspects with which I have been personally involved. In our continuing quest for understanding huge size genomic DNA, a most significant advance was effected by the discovery of restriction enzymes, leading to the production of well-defined DNA fragments, useful for physical studies as well as for molecular cloning and sequencing. Powerful tools such as gel electrophoresis, particularly pulsed field gradient gel electrophoresis, X-ray and neutron diffraction, and two-dimensional nuclear manetic resonance, not discussed in this Account, will enable molecular sorting and study of sequence-dependent local structure. Discussion of chromatin, the ultimate folding-function form of DNA,[84-86] could become the topic of a future Account.

My own contribution to this exciting field is overshadowed by that of many outstanding, intellectual contemporaries quoted in this work. It has been a privilege to contribute to an effort which has led to extraordinary advances in our understanding of the processes of life. I acknowledge with gratitude the efforts of my colleagues, quoted in joint works, who have shared my tribulations and excitement. Work of the author was supported by grants from the Israel–U.S. Binational Foundation, Jerusalem, Israel, and from the Minerva Foundation, Munich.

(82) Zaccai, G.; Wachtel, E.; Eisenberg, H. *J. Mol. Biol.* **1986**, *190*, 97.
(83) Lederer, H.; May, R. P.; Kjems, J. K.; Baer, G.; Heumann, H. *Eur. J. Biochem.* **1986**, *161*, 191.
(84) Widom, J.; Klug, A. *Cell* **1985**, *43*, 207.
(85) Felsenfeld, G.; McGhee, J. D. *Cell* **1986**, *44*, 375.
(86) Greulich, K. O.; Wachtel, E.; Ausio, J.; Seger, D.; Eisenberg, H. *J. Mol. Biol.* **1987**, *193*, 709.

Vicarious Nucleophilic Substitution of Hydrogen

MIECZYSŁAW MĄKOSZA* and JERZY WINIARSKI

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Received October 30, 1986

Nucleophilic substitution in aromatic rings is usually limited to replacement of halogens or other nucleofugal groups. This process can proceed via a variety of mechanisms: addition–elimination (S_NAr), single-electron transfer ($S_{RN}1$), formation of arynes, transition-metal catalysis, etc. In spite of the abundance of mechanistic schemes and the rich possibilities emerging therefrom, no general process for nucleophilic replacement of hydrogen was known until the end of the 1970s. Although there are quite a few earlier reports on reactions which represent nucleophilic replacement of hydrogen, in monographs and textbooks one could often find a message that nucleophilic replacement of hydrogen is rarely observed and that these examples are no more than specific cases.[1]

Professor Mieczysław Mąkosza, born in 1934 in Poland, received his M.Sc. from the University of Leningrad USSR in 1956, his Ph.D. in 1963 from the Technical University, Warsaw, and his DSc (habilitation) in 1967. In 1971, he was a postdoctoral fellow with Prof. G. A. Russell at Iowa State University. Since 1979 he has been director of the Institute of Organic Chemistry, Polish Academy of Sciences, in Warsaw. His main scientific interests include methodology of organic synthesis, reaction of carbanions and halocarbenes in two-phase systems, and nucleophilic aromatic substitution.

Dr. Jerzy Winiarski, born 1953 in Warsaw, received his M.Sc. in 1977 and his Ph.D. in 1981 from Technical University, Warsaw (with Prof. M. Mąkosza). In 1984 he was a postdoctoral fellow with Prof. J. F. Bunnett at University of California, Santa Cruz. Since 1985 he has been a research associate at the Institute of Organic Chemistry, Polish Academy of Sciences, in Warsaw.

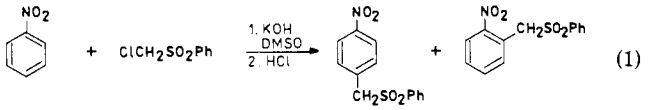
Several years ago, we started a project aimed at elaboration of a method of direct nucleophilic replacement of hydrogen in electrophilic arenes, mainly nitroarenes, in reactions with carbanions. In this endeavor, our guiding philosophy was as follows: the nucleophilic substitution of halogen, e.g., in *p*-chloronitrobenzene, proceeds via addition of a nucleophile to the ring carbon atom bearing the halogen, followed by departure of the halide anion. Since activation of the ring by the nitro group is responsible for the addition, similar addition to the ring carbon atom bearing hydrogen is also possible. It is well-known that polynitroarenes form relatively stable adducts with a variety of nucleophiles and that addition to carbon atoms bearing hydrogen is faster than to those bearing other substituents, including halogens.[2] Extrapolation of this rule to mononitroarenes leads to the assumption that, in most cases of nucleophilic aromatic substitution of halogen or other nucleofugal groups, the initial process is the fast and reversible addition of the nucleophiles to carbon atoms

(1) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968. De Boer, T. J.; Dirks, J. P. In *Chemistry of the Nitro and Nitroso Group*; Feuer, H., Ed.; Interscience: New York, 1969.
(2) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667. Terrier, A. *Chem. Rev.* **1982**, *82*, 77. Artamkina, O. A.; Egorov, M. P.; Beletskaya, I. P. *Chem. Rev.* **1982**, *82*, 4[illegible].

0001-4842/87/0120-0282$01.50/0

bearing hydrogen. The resulting adducts cannot, however, lose hydride anions; therefore, they dissociate, reverting to reactants, and the substitution of halogen takes place via slower addition to carbon atoms bearing halogens. It was therefore apparent that, in order to obtain products of the nucleophilic substitution of hydrogen, one must find a way to remove the hydrogen from the initial σ-adducts. Due to reversibility of the addition and its usually low equilibrium constant and to the sensitivity of carbanions to oxidation, treatment of the adducts with an external oxidant is unfeasible for this purpose.

We hypothesized that σ-adducts formed from carbanions containing leaving groups X (e.g., Cl) at the carbanion center could lose the leaving group X^- with simultaneous 1,2-hydride shift to give products of substitution of hydrogen with the carbanion moiety. Indeed, chloromethyl phenyl sulfone, on treatment with a strong base, reacts with nitrobenzene according to the expected stoichiometry, giving *o*- and *p*-nitrobenzyl phenyl sulfones.[3]



(1)

In this reaction, hydrogen atoms ortho and para to the nitro group are replaced with the carbanion moiety, but in fact, instead of hydrogen, the leaving group connected with the carbanion center departs from the σ-adduct. Thus, the leaving group acts here as a *vicarious* leaving group; hence, we called this reaction "*vicarious nucleophilic substitution of hydrogen*" (VNS). Further, mechanistic studies have shown that the σ-adducts are converted into the products not via hydride shift but rather by base-induced β-elimination of hydrogen chloride (or HX in general), but this mechanistic clarification does not affect the stoichiometry of the reaction.[4]

The base-induced reaction of chloromethyl phenyl sulfone with *p*-chloronitrobenzene results in exclusive replacement of the hydrogen ortho to the nitro group (eq 2). Conventional aromatic nucleophilic substitution of halogen was not observed in this case.

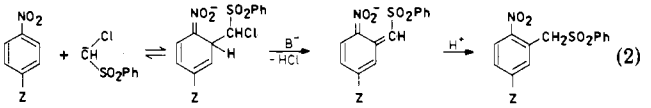
Thus, the main goal formulated above was achieved, our hypothesis was proved correct, and a new mechanism for the nucleophilic substitution of hydrogen was discovered.[5] It seems appropriate to quote here a paragraph from Joseph F. Bunnett's Account.[6] "It is not often that a new aromatic substitution mechanism of wide scope comes onto the scene. Such was the case however in my laboratory." Such also was the case in our laboratory in Warsaw in 1978. This finding resulted from a deliberate design and not from serendipitous observations.

There were a few previous reports on reactions which can be considered as early examples of VNS: methylation of nitroarenes and heterocycles with dimsylsodium[7] or with dimethylsulfoxonium methylide[8] and dichloromethylation of *p*-halonitrobenzene with trichloromethyllithium.[9] The mechanism, synthetic value, and general character of these observed reactions were not, however, recognized.

In typical vicarious nucleophilic substitution, nitroarenes react with carbanions that are usually generated in situ by action of base on the corresponding CH acids. Base is also consumed in the elimination step. It stems from this stoichiometry that at least 2 mol of base should be used per mole of the CH acid and that the products stay in the reaction mixture in the form of nitrobenzylic carbanions. They are usually highly colored (red, violet, blue, etc.), a phenomenon that has some diagnostic value. Proper selection of the base/solvent system is of great importance for the VNS: it should assure efficient deprotonation of the CH acids and fast β-elimination of HX from the intermediate σ-adduct. We have found that base/solvent systems which produce relatively free carbanions or loose ion pairs, such as KOH, NaOH, *t*-BuOK, or NaH in Me_2SO, liquid ammonia, or DMF, are necessary for VNS.

Scope

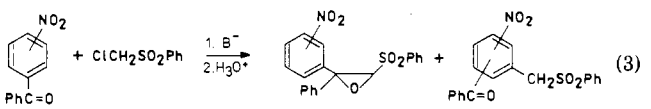
Electrophilic Arenes. For screening reactions with a variety of electrophilic arenes, chloromethyl phenyl sulfone was chosen as a model compound since it forms a relatively stable carbanion and has no tendency to self-condensation. We have found that this sulfone reacts according to the VNS scheme with nitrobenzene derivatives containing practically an unlimited variety of substituents Z located in positions ortho, meta, and para to the nitro group.[3,10] The simplest cases are 4-Z-nitrobenzenes, from which one product isomer is formed (eq 2). In cases of 2-Z- and 3-Z-nitrobenzenes, two and often three isomeric products can be produced.



(2)

Z = F, Cl, Br, I, OCH_3, OPh, SCH_3, C_2H_5, $C(CH_3)_3$, Ph, NMe_2, CF_3, CN, SO_2CH_3, COOH

Some complications were encountered in some cases. Competition from typical S_NAr replacement of Z was observed for Z = 2- or 4-F and NO_2, which are known as superior leaving groups in this process. When the substituent Z itself can react with the carbanion, this reaction can also compete with the VNS. For example, for Z = 4-PhCO, the Darzens condensation dominates. On the other hand, for Z = 2-PhCO only VNS takes place, whereas when Z = 3-PhCO, the extent of these two processes depends on the reaction conditions.[11]



(3)

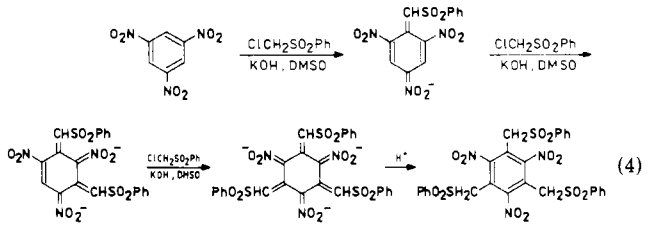
Interesting cases are nitroarenes containing acidic substituents. In strongly alkaline reaction conditions, they exist in the form of the corresponding anions. The reaction course, however, is not affected when the negative charge does not conjugate with the ring, as for example in the case of nitrobenzoic acids (Z = COO^-).[12]

(3) Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* **1978**, 3495.
(4) Mąkosza, M.; Glinka, T. *J. Org. Chem.* **1983**, *48*, 3860.
(5) Mąkosza, M. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: New York, 1983; p 401.
(6) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
(7) Russell, G. A.; Weiner, S. A. *J. Org. Chem.* **1966**, *31*, 248.
(8) Traynelis, V. J.; McSweeney, J. V. *J. Org. Chem.* **1966**, *31*, 243.
(9) McBee, E. T.; Wesseler, E. P.; Hodgins, T. *J. Org. Chem.* **1971**, *36*, 2907.
(10) Mąkosza, M.; Goliński, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.
(11) Mąkosza, M.; Goliński, J.; Baran, J.; Dziewońska-Baran, D. *Chem. Lett.* **1984**, 1619.

On the other hand, direct conjugation, as in the case of nitrophenolates, hinders nucleophilic addition and therefore nitrophenols do not enter the VNS. In all cases, VNS products are formed as nitrobenzylic carbanions; inasmuch as they also cannot add nucleophiles, the reaction is very selective in the sense of monosubstitution.

When the nitroaromatic rings contain more than one substituent, the reaction still can occur as long as there is at least one ortho or para position bearing hydrogen. Almost all the preceding discussion is applicable here; for example, VNS replacement of hydrogen in 2-chloro-5-nitro- and 4-chloro-5-nitrobenzoic acids is much faster than conventional replacement of halogen.[12]

Deactivation of nitroarenes by the negative charge conjugated with the ring can be compensated by a second nitro group. Thus, dinitrophenols, in contrast to mononitrophenols, react with the sulfone satisfactorily.[13] The accommodation of the negative charge conjugated with the ring by the second nitro group creates a possibility to afford disubstitution in *m*-dinitrobenzene and even trisubstitution in 1,3,5-trinitrobenzene.[13]

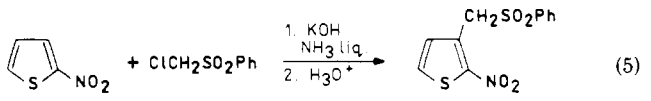


(4)

In all these cases the rates of introduction of the first, second, and third substituent are much different.

Similarly to nitrobenzene derivatives, the VNS with chloromethyl phenyl sulfone proceeds efficiently in 1- and 2-nitronaphthalenes and their derivatives. In this bicyclic ring system, substitution takes place preferentially or exclusively ortho to the nitro group at C-2 and C-1, respectively.[14]

The VNS with chloromethyl phenyl sulfone also proceeds with aromatic heterocycles containing a nitro group. Among five-membered rings, the VNS has been performed with 2- and 3-nitrothiophenes, 2-nitrofuranes, particularly substituted at C-5, and N-alkylated 2- and 3-nitropyrroles.[15]



(5)

In the latter case it is necessary to replace the N–H acidic hydrogen, since the corresponding nitropyrrole anions do not enter the reaction. The reaction also proceeds efficiently with 2-, 3-, and 4-nitropyridines.[16] In nitro heterocyclic compounds, the VNS of hydrogen proceeds much faster than conventional nucleophilic substitution of halogen located in an equally activated position. Chloromethyl phenyl sulfone reacts efficiently with 5-, 6-, and 8-nitroquinolines, replacing hydrogen exclusively or mostly "ortho" to the nitro group.[17]

Finally, some electrophilic aromatic heterocycles, even without a nitro substituent, do react with the sulfone via the VNS scheme. This was observed, for example, for acridine (at C-10), benzothiazole (at C-2), and particularly for 1,2,4-triazine.[18] In the latter case, the VNS can proceed in each of the three positions 5, 3, and 6.

Thus, one can conclude that a great number of electrophilic aromatic rings, iso- and heterocyclic, particularly those containing the nitro group, are able to enter the VNS. When there are halogen atoms located in equally activated positions, the VNS of hydrogen usually proceeds much faster than conventional nucleophilic substitution of halogen.

Carbanions. Chloromethyl phenyl sulfone was used as the model compound for studies of the scope of the VNS, since it reacts efficiently with a majority of nitroarenes. Chloromethyl *tert*-butyl sulfone,[14] phenyl and neopentyl chloromethanesulfonate,[19] and *N*,*N*-dialkyl chloromethanesulfonamide[10] are almost equally active in this reaction. Analogues of these compounds in which one methylene hydrogen is replaced with alkyl, aryl, or even halogen substitutents also react efficiently with nitroarenes according to the VNS scheme. It is, however, necessary to point out that in the latter cases in which tertiary carbanions are involved there is strong preference for or exclusive para orientation of the substitution. For all carbanions stabilized with sulfonyl groups, Cl is the most convenient and efficient leaving group. Other leaving groups are not as good, mostly because the elimination of phenylsulfinic acid can compete with the desired HX elimination. Chloride is also the most convenient leaving group for carbanions stabilized with the phenylsulfinic group[20] and also with phosphorus-containing substituents.[21] For example, (chloromethyl)diphenylphosphine oxide and diethyl (α-chlorobenzyl)phosphonate react nicely with nitroarenes to form the corresponding nitrobenzyl phosphine oxides and (nitrobenzhydryl)phosphonates.[21]

Substantial interest presents direct cyanomethylation or, in general, α-cyanoalkylation of nitroarenes via the VNS.[22,23] Since chloroacetonitrile is unstable in basic media, leaving groups such as PhO, PhS, or Me_2NCS_2 instead of Cl assure often better yields of cyanomethylation. Nevertheless, α-chloronitriles in many instances also give satisfying results, particularly with active nitroarenes (chloronitrobenzenes, nitronaphthalenes, etc.) On the contrary, α-chlorobenzyl cyanide undergoes fast self-condensation, so the corresponding phenoxynitrile should be used for α-cyanobenzylation. For α-carboalkoxyalkylation, carbanions of esters containing PhS or Me_2NCS_2 leaving groups were found to be of most general use.[23,24] Nevertheless, ethyl α-chloropropionate and α-chlorobutyrate afforded the VNS too, often in excellent yields.[25]

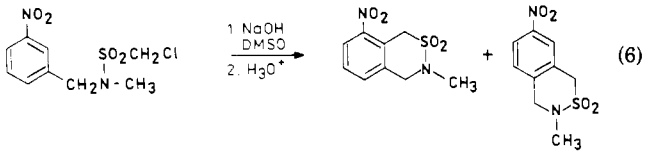
Many typical leaving groups, including Cl, PhS, etc., exert a strong carbanion stabilizing effect themselves.

(12) Mąkosza, M.; Ludwiczak, S. *Synthesis* **1986**, 50.
(13) Mąkosza, M.; Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562.
(14) Unpublished results from our laboratory.
(15) Mąkosza, M.; Słomka, E. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1984**, *32*, 69.
(16) Mąkosza, M.; Chylińska, B.; Mudryk, B. *Liebigs Ann. Chem.* **1984**, 8.
(17) Mąkosza, M.; Kinowski, A.; Danikiewicz, W.; Mudryk, B. *Liebigs Ann. Chem.* **1986**, 69.
(18) Mąkosza, M.; Goliński, J.; Rykowski, A. *Tetrahedron Lett.* **1983**, 3277.
(19) Mąkosza, M.; Goliński, J. *Synthesis* **1983**, 1023.
(20) Mąkosza, M.; Goliński, M.; Pankowski, J. *Synthesis* **1983**, 40.
(21) Mąkosza, M.; Goliński, J. *Angew. Chem.* **1982**, *94*, 468.
(22) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1980**, *45*, 1534.
(23) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494.
(24) Tanaka, A.; Usui, T. *J. Heterocycl. Chem.* **1979**, *16*, 1409.
(25) Stahly, G. P.; Stahly, B. C.; Lilje, J. C. *J. Org. Chem.* **1984**, *49*, 578.

Thus, many compounds containing such substituents, without any typical strong electron withdrawing carbanion stabilizing group, are able to enter the VNS under strongly basic conditions. Particularly interesting results were obtained with compounds containing a PhS substituent. For example, triphenylthiomethane carbanion replaces the para hydrogen in nitroarenes, giving dithioacetals of *p*-nitrobenzaldehydes.[26] The reaction of nitroarenes with carbanion of aldehyde dithioacetals gave substituted nitrobenzylic sulfides[27] whereas arylmethyl phenyl sulfide carbanions afford arylmethylation of nitroarenes.[14] The latter reaction offers a simple and unique synthesis of diarylmethanes containing electron withdrawing groups in both aromatic rings.

The trichloromethyl carbanion undergoes rapid dissociation into dichlorocarbene, but nevertheless it reacts efficiently with many nitroarenes to give the corresponding dichloromethyl derivatives. Although the latter are very unstable in basic media, they can be often isolated in excellent yields.[9,28]

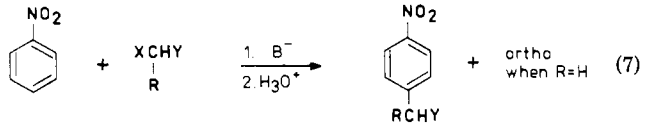
Finally, one should mention ring closure and ring opening variants of the VNS. An intramolecular reaction proceeds in the case of chloromethanesulfonamides of *m*-nitroaniline and *m*-nitrobenzylamine derivatives.[29]



(6)

An elegant application of the intramolecular VNS for a tetracycline derivative synthesis was reported by Cava.[30] A ring opening process can be exemplified by the reaction of 1-nitronaphthalene with phenylcyanooxiranes leading to cyanomethylation.[31]

In conclusion, we can state that the VNS is also a general process concerning carbanions. The main requirement is that they should contain a leaving group X connected directly to the carbanion center. The nature of the leaving group should provide the possibility of its elimination as HX from the intermediate σ-adduct. Thus, the general structure of such carbanions is $R\bar{C}XY$ where X is the leaving group, Y is the carbanion stabilizing group, and R is the substituent (eq 7). The functions assigned to the substituents X, Y, and R are of course approximate. In many cases, X and also R provide a substantial stabilizing effect; also, Y and R can be eliminated, thus acting as leaving groups.



(7)

Y = SO_2Ph, $SO_2C(CH_3)_3$, SO_2OPh, $SO_2OCH_2C(CH_3)_3$, $SO_2N(CH_2CH_2)_2O$, SOPh, $POPh_2$, $P(OEt)_2$, CN, COOR', –N=C, PhS, Cl

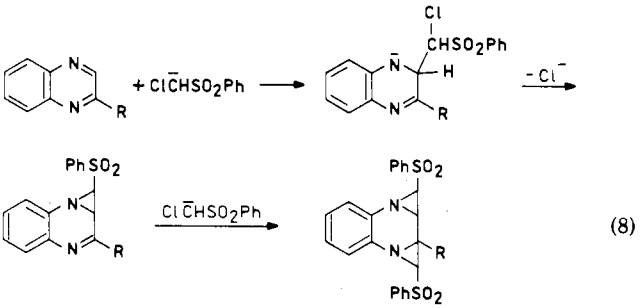
X = Cl, PhS, Me_2NCSS, PhO, CH_3O

R = H, alkyl, aryl, PhS, Cl

(26) Mąkosza, M.; Winiarski, J. *Chem. Lett.* **1984**, 1623.
(27) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 5272.
(28) Mąkosza, M.; Owczarczyk, Z. Polish Patent Appl. P-255 973, 1985.
(29) Mąkosza, M.; Wojciechowski, K. *Tetrahedron Lett.* **1984**, 4791.
(30) Murphy, R.; Cava, M. *Tetrahedron Lett.* **1984**, 803.
(31) Mąkosza, M.; Pankowski, J. *Bull. Soc. Chim. Belg.* **1985**, *94*, 235.

Almost any combination of X, Y, and R shown above produces a carbanion able to react with nitroarenes according to the VNS scheme; there are really few limitations. Nevertheless, in order to achieve desired results, such a combination should be selected meticulously. Some limitations in the selection of such combinations are due to the following: high alkylating activity of some carbanion precursors (when X = Cl self-condensation of the carbanions can compete with the VNS); ability of some groups Y (e.g., SO_2Ph) to be eliminated by basic agents; insufficient nucleophilicity or exceeding bulkiness of some carbanions, which result in difficulties in the addition or the elimination step.

Related Reactions. Attempts to extend the VNS with chloromethyl phenyl sulfone on quinoxaline resulted in a different process—formation of bis-annulated products.[32]



(8)

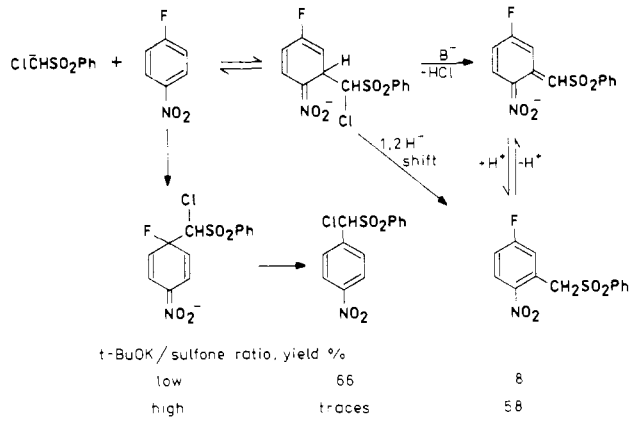
The bis annulation was found to be a reaction of quite general character—many naphthyridines and even 1-cyano- and 1-(methylsulfonyl)naphthalene reacted in a similar way.[33] In all these cases, the initial step is undoubtedly the formation of the anionic σ-adduct, which reacts further along the intramolecular nucleophilic substitution pathway giving a mono-annulated product. The latter contains an electrophilic aliphatic double bond (C=N or C=C); thus, addition of the second carbanion molecule and further annulation proceed rapidly, and a mono-annulated product cannot be obtained.

It seems that in these cases the intramolecular S_N2 reaction is preferred over the β-elimination because the negative charge in the σ-adducts is much less delocalized than in the case of nitroarenes. For this reason, the ring nitrogen or carbon atoms exhibit high nucleophilicity, and the attack of base on the ring proton leading to β-elimination is hindered. This explanation is supported by experiments with quinoxaline *N*-oxide and 6-nitroquinoxaline, which enter the VNS due to higher charge delocalization caused by an additional oxygen or electron withdrawing substituent.[14]

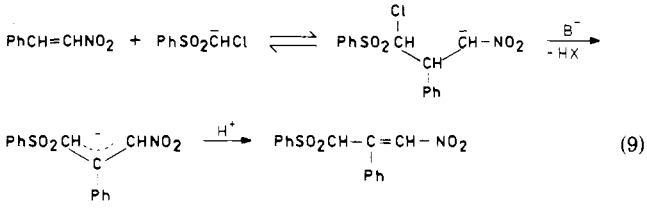
It should be mentioned that the VNS of hydrogen can also occur in the aliphatic series. Addition of a carbanion containing leaving groups to electrophilic alkenes results in the formation of the corresponding carbanionic adducts, which usually react according to the intramolecular nucleophilic substitution pattern to form cyclopropane derivatives. Nevertheless, by a proper selection of the reaction partners and conditions, we were able to enforce the β-elimination in these adducts leading to the allylic carbanions, which upon

(32) Goliński, J.; Mąkosza, M.; Rykowski, A. *Tetrahedron Lett.* **1983**, 3279.
(33) Mąkosza, M.; Glinka, T.; Ostrowski, S.; Rykowski, A. *Chem. Lett.* **1987**, 61.

Scheme I



protonation gave the desired products of the aliphatic VNS (eq 9).[34]



Mechanism

The VNS proceeds undoubtedly via formation of intermediate σ-adducts and their further transformation into products. The most feasible mechanistic pathways for the transformation of the σ-adduct into the product are departure of the leaving group X^- with simultaneous 1,2-hydride shift and base-induced β-elimination of HX. These possible pathways were differentiated by observation of the influence of base on the reaction rate. This influence was studied by using competition between replacement of hydrogen and fluorine in *p*-fluoronitrobenzene (Scheme I).[4] Rates of the formation of σ^H- and σ^F-adducts and also conversion of the σ^F-adduct into the product do not depend on the base concentration. The same should be true for conversion of the σ^H-adduct, if it proceeded via the hydride shift. On the other hand, if it proceeded via base-induced β-elimination, it should be accelerated by higher base concentration; hence, the ratio H vs. F substitution should depend on the base concentration. Since this was the case, one can exclude the hydride shift and accept the base-induced β-elimination as the mechanistic pathway of σ^H-adduct conversion.

The second conclusion that stems from these results is that the nucleophilic addition to the ring carbon atom bearing hydrogen is faster than to that bearing halogen and that the former addition, resulting in the formation of σ^H-adducts, is a reversible process. The final conclusion is that the VNS proceeds via a fast and reversible nucleophilic addition, followed by slower, base-induced β-elimination. The rate of the elimination must be nevertheless high, higher than the rate of nucleophilic addition to carbon atoms bearing halogen.

The same conclusions result from the studies of the competition between nitrobenzene and *p*-fluoronitrobenzene in the reaction with phenylphenoxyacetonitrile[4] and also from the reaction of chloromethyl phenyl sulfone with *m*-nitrobenzophenone. In the latter case, the VNS competes with the Darzens condensation; the extent of the VNS increases substantially when the concentration of base increases.[11]

Important information concerning the mechanism of the VNS came from the studies of the kinetic isotope effect. From the mechanistic picture shown above, one can suppose that it should operate on the elimination step in which C–H or C–D bonds are broken. Since the elimination is the rate-determining step for the whole process, we have expected an observable primary isotope effect for this reaction. Surprisingly, in the reaction of chloromethyl phenyl sulfone with *p*-nitrobenzene-*d*, we have found a secondary isotope effect, $k_H/k_D = 0.9$. The value of this effect was determined from differences in the ratios of ortho/para substitution in nitrobenzene and *p*-nitrobenzene-*d*.[4] The secondary isotope effect can operate on the addition but not on the elimination step; the addition step, however, does not determine the observed rate of the total reaction.

This apparent contradiction can be rationalized taking into account that the elimination occurs from a very unstable σ-adduct to a highly stabilized quinoid anion; hence, it proceeds via a very unsymmetrical, early transition state. Usually in such cases the kinetic isotope effect is close to 1. When the isotope effect of the elimination is close to unity, there is a chance to observe the secondary isotope effect on the addition step. Indeed, the addition results in rehybridization of the carbon atom from sp^2 to sp^3 and is accelerated by deuterium as compared to hydrogen. On the other hand, the dissociation of the σ-adduct should be decelerated by deuterium. As a result, the equilibrium constant of the addition to the deuteriated carbon atom is somewhat higher, and consequently the VNS of deuterium is faster than that of hydrogen. On the other hand, when the elimination proceeds via a more symmetrical transition state, as in the reaction of 2,4-dinitrobenzene-*1-d* with tertiary carbanions, the σ-adducts are better stabilized and the elimination is somewhat hindered. Thus, a typical primary isotope is observed. For example, in the reaction of α-chloropropyl and α-chlorobenzyl phenyl sulfone, k_H/k_D is 2.9 and 6.5, respectively.[14]

The general mechanistic picture is as follows. The addition of carbanions at equally activated positions of nitroarenes bearing different substituents proceeds with rates decreasing in the following order of the substituents: D > H > F > Cl. The fast formation of σ^D- and σ^H-adducts is a reversible process; the equilibrium concentration of σ^D is somewhat higher than σ^H. The fast addition is followed by slower bimolecular base-induced β-elimination leading to anions of the products.

The second important mechanistic question is whether the σ-adducts are formed via direct nucleophilic addition or via single-electron transfer (SET) followed by coupling of a radical with a radical anion. A preliminary answer to this question is based on the orientation of the VNS. The addition of the Grignard reagent to nitroarenes was shown by Bartoli to proceed via SET and radical anion coupling.[35] This mechanism

(34) Mąkosza, M.; Kwast, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1195.

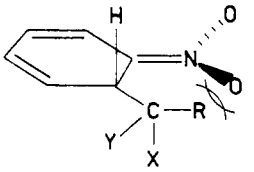
(35) Bartoli, G.; Bosco, M.; Ciminale, F.; Dalpozzo, R. *J. Org. Chem.* **1982**, *47*, 5227.

is well correlated with the orientation pattern: alkylmagnesium compounds form with nitrobenzene a mixture of ortho and para isomers in a ratio close to the statistical value of 2. Interaction of the Mg cation with the nitro group does not influence the orientation. On the contrary, in the VNS, solvation effects have a profound influence on the orientation. For example, the reaction of the sodium or potassium derivative of chloromethyl phenyl sulfone with nitrobenzene in Me_2SO, DMF, or NH_3 gave ortho and para isomers in the ratio 1–1.5, whereas the potassium derivative in THF reacts with nitroarenes selectively ortho to the nitro group (vide infra).[36] Thus, the orientation is determined by the polar effect. Carbanions, not free radicals, add to the ring, and the σ-adducts are formed via direct addition rather than via SET. This conclusion is supported by the test with the so-called radical clock. In some preliminary experiments, we have found that 1-chloro-5-hexenyl phenyl sulfone enters the VNS with nitrobenzene and some other nitroarenes without competing cyclization. Although on this basis we prefer direct nucleophilic addition over the SET pathway for the formation of the σ-adducts, this question awaits a final answer.

Orientation

The VNS is a two-step reaction which proceeds via a fast and reversible formation of the σ-adducts, followed by a slower base-induced β-elimination. Therefore, the rates of the substitution of hydrogen in different positions depend on the concentration of the isomeric σ-adducts and the rate constants of the elimination of HX from these adducts. Taking into account that carbanions themselves are strong bases too and that their concentration changes during the reaction, the total picture is quite complicated. From a phenomenological standpoint the orientation depends on three factors: structure of the carbanions, structure of the arenes, and the reaction conditions.

Structure of Carbanions. It has already been mentioned that the ortho/para ratio of the VNS in nitrobenzene with α-haloalkyl aryl sulfones is highly sensitive toward steric factors: secondary carbanions $X\bar{C}HSO_2Ar$ react in both positions, the ortho/para ratio decreases in the order X = F, Cl, Br, I, whereas tertiary carbanions $X\bar{C}RSO_2Ar$ (R = Me, Ph, Cl) react only in the para position.[3,10] Similar high sensitivity of the orientation to the steric factors was observed for other carbanions. Lack of ortho substitution in the reaction of nitrobenzene with tertiary carbanions does not mean impossibility of such a process. When the para position in nitroarenes is blocked or is sterically hindered by a substituent meta to the nitro group, some tertiary carbanions can react satisfactorily at the ortho position.[37] Steric hindrance in the VNS can operate on both steps: addition and elimination. Taking into account that S_NAr of halogens is not very sensitive to primary steric hindrance,[1] the addition step in the VNS should not be either. On the other hand, there is a good reason to suppose that the elimination step is very sensitive to steric effects, for reasons shown below.



The lower rate constant of the elimination caused by steric hindrance can be compensated by higher concentration of the σ-adducts due to the presence of an additional electron withdrawing substituent, e.g., NO_2, CF_3, COOR, etc., and higher nucleophilicity of tertiary carbanions (R = CH_3, C_2H_5).[14]

Conditions. Under the conditions most favorable for the VNS, in which carbanions form loose ion pairs (Na or K derivatives in Me_2SO, DMF, or NH_3), the ortho/para ratio is governed by the kind of carbanion and does not depend substantially on the kind of cation and solvent. It should be noted, however, that under such conditions changes in procedure, for example order of mixing or concentration, can affect this ratio. On the other hand, *t*-BuOK/THF base/solvent system provides a unique possibility to afford selective ortho orientation in the VNS with many secondary carbanions. This strong effect was observed in the reaction of a variety of nitroarenes with chloromethyl phenyl sulfone[36] and acetonitrile derivatives.[37] Under these conditions, the carbanions are in the form of tight ion pairs with potassium cations which are attracted by the negatively charged oxygen atoms of the nitro groups. Consequently, σ-adducts are formed in the ortho position. Addition of an equivalent of a crown ether eliminates this effect.[36]

Structure of the Arenes. Two effects should be taken into consideration: structure of the aromatic ring and the influence of substituents. In comparison with the nitrobenzene ring as a reference, the orientation (ortho/para ratio) in the nitropyridines does not differ significantly. In other less symmetrical systems, the situation is different. In bicyclic nitroarenes such as nitronaphthalenes[14] and nitroquinolines[17] the reaction proceeds mainly or exclusively "ortho" to the nitro group. In the case of 1-nitronaphthalene and 5- and 8-nitroquinolines, higher double-bond character of 1,2-5,6-, and 7,8-bonds causes preferential ortho addition (at positions 2, 6, and 7, respectively). Some steric effects of peri hydrogen atoms can enhance this tendecy. 2-Nitronaphthalene and 7- and 6-nitroquinolines react exclusively at positions 1, 8, and 5.

In five-membered heterocycles, the high double-bond character of 2,3-and 4,5-bonds is widely used for explanation of the relative rates of the nucleophilic replacement of halogens in 2-nitro-3-halo and 5-halo derivatives.[38] The same arguments can be used in the VNS in order to explain the high tendency for 3-substitution in 2-nitro derivatives. Additionally, the "ortho" substitution is favored by the geometry of five-membered rings, due to which steric hindrance in the addition and elimination steps is less important than in six-membered rings.

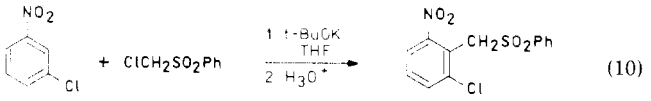
Influence of Substituents Z in the Nitroaromatic Ring. In 4-Z-nitrobenzenes, the reaction can only proceed ortho to the nitro group. In 2-Z-nitrobenzenes, the substituent Z affects the ortho/para ratio mainly

(36) Mąkosza, M.; Glinka, T.; Kinowski, A. *Tetrahedron* **1984**, *40*, 1863.

(37) Mąkosza, M.; Wenäll, M.; Goliński, M.; Kinowski, A. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1985**, *33*, 427.

(38) Spinelli, D.; Guanti, G.; Del'Erba, J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 441.

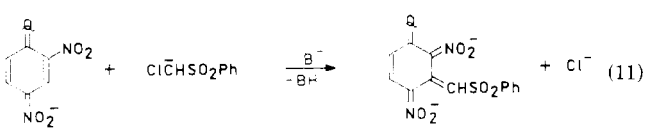
due to the statistical factor. The most interesting are the cases of 3-Z-nitrobenzenes. Here, three isomeric products of substitution at positions 2, 4, and 6 can, in principle, be formed. The proportion of these isomeric products depends on the nature of Z and also on the kind of carbanion and the conditions. Thus, the picture is quite complicated. Taking into account the orienting effect in the reaction with our model chloromethyl sulfone, substituents Z can be divided into two main groups (1) favoring and (2) disfavoring the reaction in their vicinity (at positions 2 and 4). To the first group belong F, Cl, Br, I, CH_3, CH_3O, etc.; to the second, CF_3, COOR, COR, NO_2.[36] A similar orientation pattern is observed in the reaction with some other secondary carbanions. Combination of the effect of the first group of substituents Z and the conditions favoring ortho orientation results in preferential substitution at the most hindered position 2, for example



(10)

The nature of the substituent effect is very complicated since it embraces its influence on the addition and also the elimination step. There is some correlation of the orientation with LUMO orbitals coefficients,[14] and a somewhat better rationalization can be based on classical electronic effects, but all these discussions are limited to the addition step.

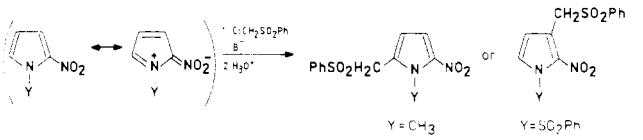
Very interesting and better understood are effects of strong electron donating substituents. As has been mentioned, dinitrophenols enter the reaction, obviously in the form of the corresponding phenolates. In 2,4-dinitrophenolate, the substitution takes place at position 3 ("between" the nitro groups) in sharp contrast to 1,3-dinitrobenzene and 2,4-dinitroanizole where it proceeds at positions 4 and 5, respectively. This surprising orientation is due to the structure of the dinitrophenolate anion, which can be considered as nitrocyclohexadienone nitronate anion; thus, the nucleophilic addition should occur at position 3.[13] For the same reason, disubstitution in 1,3-dinitrobenzene results in entering of the second substituent in position 2 (eq 11). A similar explanation is valid for the 3-substitution in 2,4-dinitroaniline and its *N*-methyl and *N*-phenyl derivatives, which under strongly alkaline reaction conditions form the corresponding anions. Nevertheless, in *N*,*N*-dimethyl-2,4-dinitroaniline, the substitution also takes place at C-3. This orientation can be explained by using the concept of the dipolar structures widely applied for rationalization of physical properties of nitroanilines.



(11)

Q = O, NH, N–CH_3, NPh, $CHSO_2Ph$, $\overset{+}{N}Me_2$

This explanation is strongly supported by the exclusive 5-orientation in *N*-methyl-*N*-benzoil-2,4-dinitroaniline, in which the electron pair of the amino group cannot be efficiently conjugated with the nitro group.[14] A similar type of effect is probably responsible for the orientation in 1-methyl-2-nitropyrrole. In analogy to 2-nitrothiophene and 2-nitrofurane, we have supposed that in this case the VNS also proceeds at position 3.[15] More exact analysis revealed that in fact the 5-isomer was formed.[14] Perhaps contribution of the resonance structure as in eq 12 is responsible for this orientation. This hypothesis is supported by the exclusive formation of the 3-isomer in the reaction of 1-(phenylsulfonyl)-2-nitropyrrole with chloromethyl phenyl sulfone.[14]



(12)

General Remarks and Conclusions

The VNS discussed in this Account is a general process by which hydrogen atoms in electrophilic arenes can be replaced with α-functionalized carbon substituents. From a stoichiometric point of view, the VNS is analogous to the Friedel–Crafts reaction because in both these reactions precursors containing halogens or other leaving groups are used. This similar stoichiometry is, however, connected with reverse polarity of the reaction course. The Friedel–Crafts reaction proceeds by electrophilic attack of a carbocation on a nucleophilic aromatic ring, resulting in the formation of a cationic σ-adduct, whereas the VNS proceeds via nucleophilic attack of a carbanion on an electrophilic ring, giving an anionic σ-adduct. It is therefore justified to apply the term umpolung, introduced by Prof. D. Seebach, in order to specify reverse polarity of reactants, and consider the VNS as umpolung of the Friedel–Crafts reaction. It is also noteworthy that the VNS is a process complementary to the Friedel–Crafts reaction. It proceeds with those aromatic systems which do not enter (or are very inert) in Friedel–Crafts reaction. Therefore, it is presently possible to afford replacement of hydrogen with functionalized alkyl substituents in nearly every aromatic ring.

On the basis of our results and existing data, we would like to make a generalization concering reactions of nucleophiles with electrophilic arenes. It seems well documented that in these systems σ^H-adducts are initially formed in a fast and reversible (in principle) process. There are many ways in which these σ^H-adducts can be further converted into products.

1. Oxidation with external oxidants: This process is possible when (a) nucleophiles are resistant toward oxidation as, for example, OH^-, NH_3,[39] (b) the equilibrium constant for the addition is high due to high electrophilicity of arenes, e.g., polynitroarenes,[40] or (c) the equilibrium constant is high due to additional stabilization of the σ-adducts by specific interaction with cations (addition of RMgX,[41] RLi[42]) or stabilization by O-silylation of the adducts.[43] Oxidation is also advantageously exercised via addition of Br_2 followed by elimination of HBr.

(39) (a) Malykhin, E. W.; Shtark, A. A.; Shteingartz, W. D. *Zh. Org. Khim.* **1982**, 1838. (b) de Bie, D. A.; Geurtsen, B.; van der Plas, H. C. *J. Org. Chem.* **1985**, *50*, 484.
(40) King, T. J.; Newall, C. E. *J. Chem. Soc.* **1962**, 367.
(41) Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109.
(42) Kienzle, F. *Helv. Chim. Acta* **1978**, *61*, 449.
(43) RajanBabu, T. V.; Reddy, G. S.; Fukunaga, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 5473.

2. Conversion to nitroso compounds: Under favorable conditions (protic media) the σ-adducts of some nucleophiles are converted into nitroso compounds. The latter are very active and undergo a variety of interesting transformations.[44]

3. Vicarious nucleophilic substitution: This occurs when nucleophiles, particularly carbanions, contain leaving groups X that can be eliminated as HX. This reaction is the main subject of this Account. Amination of some nitroarenes with hydroxyloamine and aminotriazole in basic medium also belongs to the category.[45]

4. Annulation: This process occurs when, in σ-adducts of carbanions containing leaving groups, the negative charge is less delocalized.[32,33]

5. ANRORC reaction: In many heterocycles containing leaving groups X, σ-adducts undergo ring opening, HX elimination, and ring closure. The final results are often identical with conventional nucleophilic replacement of X, but in fact H is replaced.[46]

6. There are many variants of "cine" and "tele" substitutions in which σ-adducts are further converted via elimination of leaving groups from different positions.[47]

Only when the structures of the arenes and the nucleophiles and also the conditions are such that none of these (or similar) reactions can proceed with a sufficient rate, then, due to reversibility of the σ^H-adducts formation, slower formation of the σ^X-adducts leads to the conventional nucleophilic replacement of halogen via the S_NAr mechanism. We can therefore claim that this well-known and important reaction is in fact a secondary process.

This work was supported by the Polish Academy of Sciences Grant CPBP 01.13.

(44) Davis, R. B.; Pizzini, L. C. *J. Org. Chem.* **1960**, *25*, 1884. Mąkosza, M.; Jagusztyn-Grochowska, M.; Ludwikow, M.; Jawdosiuk, M. *Tetrahedron* **1974**, *30*, 3723. Mąkosza, M.; Danikiewicz, W. *J. Chem. Soc. Chem. Commun.* **1985**, 1792.

(45) Price, C. C.; Voong, S.-T. *Organic Synthesis*; Wiley: New York, 1955; Collect. Vol. III, p 664. Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039.

(46) Van der Plas, H. C. *Tetrahedron* **1985**, *41*, 237.

(47) Self, D. P.; West, D. E.; Stirling, M. R. *J. Chem. Soc., Chem. Commun.* **1980**, 281.

Control of the Catalytic Activity of Prosthetic Heme by the Structure of Hemoproteins

PAUL R. ORTIZ DE MONTELLANO

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143

Received February 9, 1987 (Revised Manuscript Received May 8, 1987)

The three general biological functions of hemoproteins are the transport of electrons (e.g., cytochrome b_5), the transport of oxygen (e.g., hemoglobin), and the catalysis of redox reactions (e.g., cytochrome P450, horseradish peroxidase). Despite the differences in the chemistry they support, all of these proteins have iron protoporphyrin IX (heme) as their prosthetic group. Their different functions therefore stem from differences in the way the protein interacts with the heme and with potential substrates. The mechanisms by which the protein controls the intrinsic reactivity of the heme are of both theoretical and practical interest. The heme in the electron carrier hemoproteins is exceptional in that it has two strong axial ligands and generally does not bind molecular oxygen or peroxides. The heme in all the other hemoproteins has one accessible coordination site which allows it to bind and react with peroxides and other ligands (Figure 1). The reaction of ferric hemoproteins with peroxides results in cleavage of the oxygen–oxygen bond and oxidation of the iron to the ferryl [Fe^{IV}=O] state. If the peroxide bond is cleaved heterolytically, as it usually is, the one-electron change in iron oxidation state is paralleled by oxidation of the porphyrin to a radical cation (e.g., horseradish peroxidase) or a protein residue to a radical species (e.g., cytochrome *c* peroxidase).[1-3] Cytochrome P450 is unique among the hemoproteins in that it can react with peroxides but usually reduces molecular oxygen to generate its own peroxide equivalent. It is not known whether the Fe^{IV}=O species presumed to be the active oxidant of cytochrome P450 is matched by a porphyrin or protein radical. These mechanistic alternatives are illustrated schematically in Figure 1. Once activated, the oxygen of the ferryl complex ($[FeO]^{3+}$) can be transferred to a substrate (RH) or can simply abstract one or more electrons from the substrate (P$^\bullet$ stands for a porphyrin or protein radical):

$$PFe^{IV}{=}O + R^\bullet + H^+ \leftarrow P^\bullet Fe^{IV}{=}O + RH \rightarrow PFe^{III} + ROH$$

Electron abstraction is characteristic of the peroxidases and oxygen transfer of the cytochrome P450 monooxygenases, but it is not unusual for hemoproteins to function, at least in the test tube, in more than one of these catalytic modes.

The Active Site of Cytochrome $P450_{cam}$. Cytochrome $P450_{cam}$, in contrast to eukaryotic cytochrome

Paul R. Ortiz de Montellano received his undergraduate and graduate education at MIT and Harvard, respectively. He is currently Professor of Chemistry, Pharmaceutical Chemistry, and Pharmacology at the University of California in San Francisco and his research interests are in the areas of enzyme mechanisms, hemoproteins, and toxicology. His principal collaborators on Saturday afternoons are Bellini, Bolto, Gounod, and Verdi.

(1) Dunford, H. B.; Stillman, J. S. *Coord. Chem. Rev.* **1976**, *19*, 187–251.

(2) King, N. K.; Looney, F. D.; Winfield, M. E. *Biochim. Biophys. Acta* **1967**, *133*, 65–82.

(3) Yonetani, T.; Schleyer, H. *J. Biol. Chem.* **1967**, *242*, 1974–1979.

0001-4842/87/0120-0289$01.50/0