

reaction proceeded, probably by way of an analogous electron-transfer process, 70, to give large-size ring systems 71 ($n = 12$; acetone-petroleum ether).⁴⁸ The search for new donor-acceptor pair systems continues.^{10b,49}

Type I and Other Reactions

Photolysis of *N*-ethyl-*d*-camphorimide (72) furnished a product, 74, of a different pattern as well as the expected bridged keto lactams 73.³⁴ The pathway leading to 74 may involve α cleavage of the photoelimination product followed by hydrogen transfer in the intermediate biradical 75, in which a radical is stabilized on the tertiary carbon (Scheme XII).³⁴ This is a typical case of the type I process found in imide photochemistry.

Miscellaneous photoreactions of cyclic imides include decarboxylation of *N*-phthaloyl- α -amino acids⁵⁰ and dearomatization of 4-methylphthalimide derivatives.⁵¹ Evidence for oxetane formation in the cyclic imide system is accumulating.^{10c,18,49} Such oxetane formation, both intra- and intermolecular, is a subject of current interest. Cyclizations, probably initiated by electron transfer,^{36,45,49,52} are also being pursued.

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(49) K. Maruyama, Symposium on Photochemistry, Sendai, Nov 1977, Abstracts of Papers, p 212.

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Conclusion

One section of the still growing array of photoreactions of carbonyl derivatives is based on the diverse photochemical behavior of cyclic imides. Mechanistic studies are still in their infant stage. However, in general, the effects of nitrogen and the second carbonyl appear to compensate each other. Therefore, in a rough and simple approximation, preliminary synthetic designs would consider aliphatic imides as aliphatic ketones, and aromatic imides as aromatic ketones. Photoreactions of alicyclic imides are highly efficient. In aromatic cyclic imides, the benzenoid system behaves as a good electron acceptor, and selection of substituents would broadly vary and improve their acceptor capability of the benzenoid system and consequently their photoreactivity. The search for suitable combination of functionalized substrates in the light of the working hypothesis of the "donor-acceptor pair system" will catalyze synthetic attempts, not only in the cyclic imides but also in the field of organic reactions at large. In this Account I hope to have shown that novel features and unexpected variations in synthetic photochemistry can be introduced as a function of the complexity of molecular structures and that continued research in this area therefore is still worthwhile.

I wish to express my gratitude to my co-workers whose names appear in the references for their efforts that have culminated in this Account. I am grateful to Dr. B. Witkop, with whom I had worked many years ago and shared some of the work cited here, for valuable advice and perusal of the manuscript. Thanks are also due to Professor K. Maruyama for discussions and preprints. Financial support from the Ministry of Education, Science and Culture, Japan, is gratefully acknowledged.

Aromatic Substitution by the *S_{RN}1* Mechanism

JOSEPH F. BUNNETT

University of California, Santa Cruz, California 95064

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Aromatic substitution reactions have been known for a long time, at least since the first nitration of benzene by Mitscherlich¹ in 1834. Many of them are workhorses of synthetic chemistry, and most of them occur by one of a small number of extensively studied mechanisms. 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 in Santa Cruz in 1970.

Actually, what we found² was that aromatic substitution can occur by a mechanism recognized 4 years earlier, by Nathan Kornblum³ and Glen Russell⁴ and their respective co-workers, for substitutions at certain aliphatic sites, especially for reactions of nucleophiles

with *p*-nitrobenzyl chloride and 2-chloro-2-nitropropane. My collaborators and I have found their mechanistic hypothesis to serve excellently, without any need for revision in its essential features, for prediction and interpretation of a wide range of phenomena never visualized when the mechanism was formulated in 1966.

However, I do not think that if we had set out intentionally to extend their observations to include substitutions at aromatic sites we would have been successful. We have subsequently found the nucleo-

(1) E. Mitscherlich, *Ann. Pharm.*, **9**, 39 (1834); *Ann. Phys.*, **31**, 625 (1835).

(2) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463, 7464 (1970).

(3) (a) N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.*, **88**, 5662 (1966); (b) before 1966, R. C. Kerber, G. W. Urry, and N. Kornblum (*J. Am. Chem. Soc.*, **86**, 3904 (1964); **87**, 4520 (1965)) proposed a nonchain radical mechanism similar in some respects to the 1966 mechanism, significantly different in others. Their 1964-1965 hypothesis resembled a mechanism proposed by F. M. Beringer, S. A. Galton, and S. J. Huang (*ibid.*, **84**, 2819 (1962)) for the phenylation of certain carbanions by diphenyliodonium ion.

(4) G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, **88**, 5663 (1966); **90**, 347 (1968).

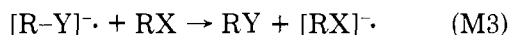
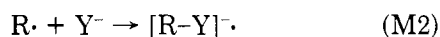
Joseph F. Bunnett is a native of Oregon, educated at Reed College (B.A., 1942) and the University of Rochester (Ph.D.). He has taught at Reed College, the University of North Carolina, Brown University, and since 1966 at the University of California, Santa Cruz. His research has largely concerned mechanisms of reactions of aromatic compounds, especially with basic or nucleophilic reagents. He is editor of *Accounts of Chemical Research*.

philes that figured prominently in their work (especially nitronate ions and anions of β -dicarbonyl compounds) to be ineffective in aromatic $S_{RN}1$ reactions. Also, nitro substituents were invariably present in their early studies, but $S_{RN}1$ reaction with a nitroaryl halide has yet to be recognized.

Though we have been most interested in continuing studies of aliphatic substitution by this mechanism, especially in Kornblum's laboratory,⁵ we consider its most intriguing and important manifestations to be in substitutions at aromatic sites.

The $S_{RN}1$ Mechanism. The mechanism to which I refer is a radical chain mechanism of nucleophilic substitution. As such it necessarily involves initiation, propagation, and termination steps. If the chain is long, most of the reaction occurs in the propagation steps, and they are sketched in generalized notation in Scheme I.

Scheme I



This mechanism involves three types of reactive intermediates, radical $R \cdot$ and radical anions $[RX]^- \cdot$ and $[RY]^- \cdot$. Generation of any one of them will provide entry into the propagation cycle.

In step M1 of the propagation cycle, radical anion $[RX]^- \cdot$ fragments to form radical $R \cdot$ and anion X^- . This type of fragmentation is known in other contexts.^{6,7} In step M2, radical $R \cdot$ combines covalently with nucleophile Y^- to form radical anion $[RY]^- \cdot$. If Y^- were identical with X^- , step M2 would be the reverse of M1. Reactions of the type of step M2 have been separately observed.^{8,9} Step M3 is an electron transfer, from radical anion $[RY]^- \cdot$ to substrate RX . Electron transfers from the radical anions of aromatic hydrocarbons to aromatic hydrocarbon molecules are well-known.¹⁰

Summation of the three steps of Scheme I gives the equation: $RX + Y^- \rightarrow RY + X^-$. Thus, although the mechanism involves radical and radical anion intermediates and an electron-transfer step, its effect is nucleophilic substitution.

When I first read the communications of Russell⁴ and of Kornblum,^{3a} I was fascinated but I found the new mechanism hard to remember. Then I recognized that steps M1 and M2 are just like the two steps of the familiar S_N1 mechanism, except that the principal substrate-derived species are one electron richer. Accordingly, in 1970 Kim and I² proposed the symbol $S_{RN}1$ to acknowledge the similarity to the S_N1 mechanism but also point to the intermediacy of radicals. The earlier workers had given the mechanism no handy name or symbol.

Discovery. Our recognition of aromatic substitution by the $S_{RN}1$ mechanism² was serendipitous. We had

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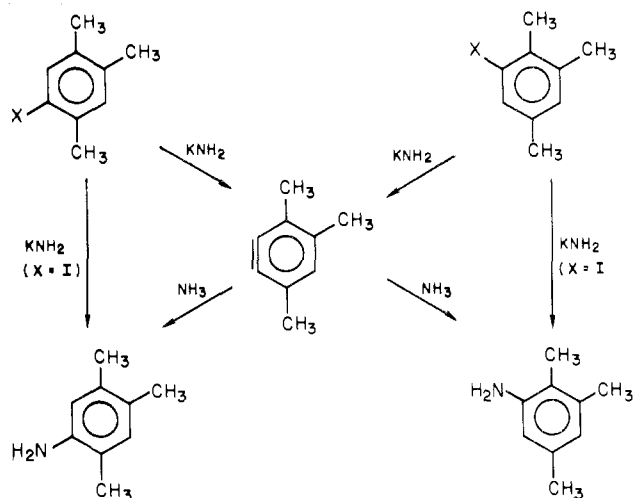
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Scheme II



submitted three 5-halo- and three 6-halopseudocumenes, the halogens being chlorine, bromine, and iodine, to the action of KNH_2 in ammonia, anticipating reaction by the aryne mechanism.^{2,11} Inasmuch as all six substrates should give the same aryne, regardless of the position or identity of the halogen (Scheme II), all were expected to give the same product ratio of 6-amino- to 5-aminopseudocumene. That expectation was fulfilled insofar as the chloro and bromo substrates were concerned; all four gave a 6- NH_2 /5- NH_2 product ratio of 1.46. However, the 5- and 6-iodo substrates gave product ratios of 0.63 and 5.9, respectively, both representing enrichment in unrearranged product, as compared to the "aryne" product ratio of 1.46. Clearly, a nonrearranging substitution mechanism was in competition with the aryne mechanism. We considered the S_NAr mechanism^{12,13} to be unlikely, but thought the $S_{RN}1$ mechanism to be a possibility.

Our attitude toward that mechanism changed from interest to conviction when we found, first, that a radical scavenger (tetraphenylhydrazine) largely suppressed the nonrearranging component of the reactions of 5- and 6-iodopseudocumenes, and second, that the addition of potassium metal steered substitution *entirely* to unrearranged products.² Potassium metal dissolves in ammonia to furnish, prominently, potassium cations and solvated electron anions. Combination of solvated electrons with aryl halide molecules (eq 1)



forms aryl halide radical anions, which can enter the $S_{RN}1$ propagation cycle at step M1.

The Scope of Aromatic $S_{RN}1$ Reactions

Our conviction as to the viability of the $S_{RN}1$ mechanism gave us courage to try unprecedented reactions under conditions not usually employed for aromatic nucleophilic substitutions. Knowing the limitations of the familiar S_NAr and aryne mechanisms, we foresaw the possibility that reactions by a new mechanism, suitably provoked, would enable conversions to be accomplished that are practically impossible when the more familiar mechanisms prevail. These

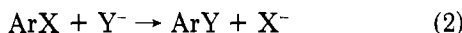
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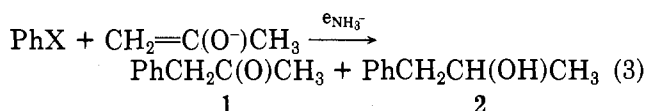
anticipations were rewarded. Several new reactions were found. Reactivity in *S_{RN}1* reactions obeys a unique set of rules, though at the outset we did not know what they were.

As to the scope of aromatic *S_{RN}1* reactions, several questions came to mind. Letting eq 2 represent such



a reaction in general, we asked what nucleophiles (Y^-) might be employed, what nucleofugic groups ($-\text{X}$) would be workable, what kinds of aromatic systems ($\text{Ar}-$) would accede to this type of mechanism, what nonparticipating substituents would be compatible with it, and how this radical chain mechanism might be initiated.

Initiation. We saw above (cf. eq 1) the efficacy of solvated electrons supplied by alkali metals in ammonia. Most of our experience with solvated electron initiation relates to reactions with three nucleophiles: amide ion,^{2,14} acetone enolate ion^{15,16} (eq 3), and cyanomethyl



anion.^{17,18} Provided that the nucleophile does not react spontaneously with the substrate (as does KNH_2 with many aryl halides, to form arynes), one can conduct such reactions by dropping bits of alkali metal into a solution of the nucleophile and substrate in ammonia, allowing the blue color from one bit to disappear before adding the next.

Many aromatic *S_{RN}1* reactions occur superbly under photostimulation.¹⁹ We generally conduct such reactions in Pyrex flasks in a simple commercial photochemical reactor that utilizes fluorescent lamps emitting maximally at 350 nm, with irradiation times varying from a few minutes to 3 h.

One would anticipate that electrons supplied from a cathode would also initiate *S_{RN}1* reactions, much as in eq 1. Such has indeed been observed; *p*-bromobenzophenone and thiophenoxide react, in CH_3CN in the vicinity of a cathode, to form *p*-(phenylthio)-benzophenone in 80% yield.²⁰

Some aromatic *S_{RN}1* reactions occur spontaneously in the dark, at room temperature or lower.^{2,21,22}

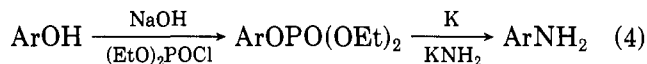
Nucleofugic Groups. In reactions of several monosubstituted benzenes with acetone enolate ion stimulated by solvated electrons¹⁵ (eq 3), fair to excellent yields of phenylacetone (1) and 1-phenyl-2-propanol (2) were obtained when the nucleofugic group was I, Br, Cl, F, SPh, NMe_3^+ , or $\text{OPO}(\text{OEt})_2$. These seven nucleofugic groups have first atoms representing seven elements, and eq 3 constitutes a method for

installing a carbon chain on an aromatic ring in place of any of them. Many of those seven have been involved in other aromatic *S_{RN}1* reactions. However, it is to be noted (see below) that in photostimulated reactions reactivity is sometimes sharply dependent on the identity of the nucleofuge. Some are for practical purposes unworkable.

In exploratory studies of reaction 3, attention was given to several monosubstituted benzenes with other nucleofugic groups. Some were cleaved to yield benzene but furnished no 1 or 2. Substrates showing this behavior include benzenesulfonate ion, triphenylphosphine, and diphenyl sulfone.²³

The *S_{RN}1* replaceability of trimethylammonio and diethyl phosphate groups has special implications for synthesis. Inasmuch as the conversions $\text{ArNO}_2 \rightarrow \text{ArNH}_2 \rightarrow \text{ArNMe}_3^+$, and $\text{ArOH} \rightarrow \text{ArOPO}(\text{OEt})_2$, are easily performed in high yield, it follows that aromatic nitro compounds, aromatic primary amines, and phenols may be considered as potential reagents for the arylation of many carbanions and other nucleophiles.

This concept has its greatest novelty in respect to phenols. Conventionally, a phenolic hydroxyl group is pretty much a dead end in synthetic chemistry. One can be sure alkylate or acylate a phenol, but what else? Now phenols (through their diethyl phosphate esters) are to be classed as potential reagents to arylate nucleophiles. An illustration (see eq 4) is a convenient



method for converting phenols to aromatic primary amines.¹⁴ (*A note of caution:* some $\text{ArOPO}(\text{OEt})_2$, notably *p*-nitrophenyl diethyl phosphate, are highly toxic.)

The diazonio group ($-\text{N}_2^+$) of diazonium salts might be expected to be a suitable nucleofuge. Diazonium salts readily accept electrons, being converted into short-lived arylazo radicals ($\text{Ar}-\text{N}=\text{N}\cdot$),²⁵ from which aryl radicals are formed by loss of dinitrogen. Mechanisms with propagation sequences similar to that of Scheme I have been proposed for the reaction of *m*-nitrobenzenediazonium ion with nitrite ion to form *m*-dinitrobenzene²⁴ and for the reactions of diazonium salts with iodide ion to form aryl iodides.²⁶

Aromatic Substituents. Having no requirement for activation by other substituents (in contrast to *S_NAr* reactions), aromatic *S_{RN}1* reactions occur satisfactorily with simple phenyl halides. The mechanism is tolerant of alkyl and alkoxy groups, as well as of phenyl, carboxylate ($-\text{COO}^-$), and benzoyl substituents.^{27,28} However, dimethylamino, ionized hydroxy ($-\text{O}^-$) and nitro groups characteristically interfere.^{27,28}

In aromatic *S_{RN}1* reactions, the nucleophile invariably occupies the position vacated by the nucleofuge. This contrasts with substitution by the aryne mechanism, in which cine substitution often occurs.

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(18) R. A. Rossi, R. H. de Rossi, and A. F. Lopez, *J. Am. Chem. Soc.*, **98**, 1252 (1976).

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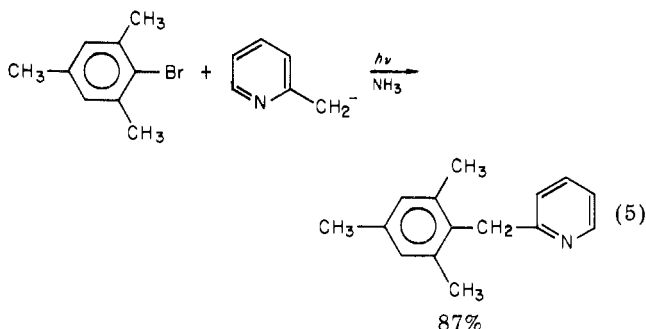
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Aromatic $S_{RN}1$ reactions are remarkably insensitive to the steric effects of ortho substituents. Mesityl bromide or iodide may be employed to mesitylate nucleophiles in good yield; see eq 5, for example.²⁹



Even the reaction of 1-iodo-2,4,6-triisopropylbenzene with acetone enolate ion, photostimulated, gives a significant amount of substitution product.

When two nucleofugic groups are present, as in dihalobenzenes (vide infra), one or both may be replaced, depending on their identity, their orientation, and the identity of the nucleophile.

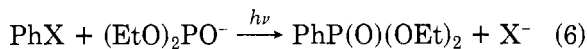
Aromatic Systems. Halonaphthalenes have often been observed to participate in $S_{RN}1$ reactions.^{18,27,28,30,31} 9-Bromophenanthrene and 9-bromoanthracene react satisfactorily with acetone enolate ion.²⁷ Apparently aromatic $S_{RN}1$ reactions occur in polynuclear aromatic systems in general.

Wolfe and associates have shown that they also take place with halogen derivatives of pyridine and quinoline,³²⁻³⁵ and indeed more readily than with phenyl halides. $S_{RN}1$ reactions occur with halogen derivatives of isoquinoline,³⁶ and (apparently) of other nitrogen heterocycles.³⁷ With halothiophenes, they occur but less readily than with phenyl halides.³⁸

Certain vinylic halides have been observed to undergo substitution apparently of $S_{RN}1$ character.³⁹

Nucleophiles. Several types of carbanions, several types of phosphanions, thiolate ions, amide ion (NH_2^-), and benzeneselenolate ion ($PhSe^-$)⁴⁰ have been found to participate in aromatic $S_{RN}1$ reactions. Carbanions of the ketone enolate^{15,16,18,19,21,27,32-35,41} and ester enolate^{42,43} types, α -cyanoalkyl anions,^{17,18,28} and such ions as picolyl anions²⁹ (see eq 5) and the conjugate bases of fluorene, anethole, and 1,3-pentadiene¹⁶ all react very well with suitable substrates.

The prototype reaction of a phosphanion nucleophile is that of diethyl phosphite ion with iodo- or bromobenzene³¹ (eq 6). With aryl iodides, this reaction occurs



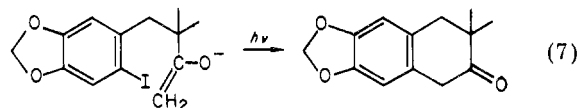
rapidly in virtually quantitative yield on a preparative scale⁴⁴ and has special synthetic interest because most other methods for establishing phosphorus functionalities at aromatic sites are difficult or circuitous. Other phosphanions that react satisfactorily are $(EtO)_2PS^-$, Ph_2PO^- , $PhP(OC_4H_9)O^-$, $(Me_2N)_2PO^-$, and Ph_2P^- .⁴⁵

Among sulfanions, arenethiolate^{30,36,46} and alkane-thiolate ions^{18,47} are effective nucleophiles in aromatic $S_{RN}1$ reactions. Reactions of the latter are sometimes complicated by fragmentation of intermediates⁴¹ (vide infra).

To date the only nitranion nucleophile recognized to participate satisfactorily is plain amide ion (NH_2^-).^{2,14}

Nucleophiles that appear to be unreactive in aromatic $S_{RN}1$ reactions include benzenesulfinate ion, alkoxide ions, phenoxide ion, and stabilized carbanions such as those from malonic ester and nitromethane.^{34,41} However, dianions from suitable 1,3-diketones, such as from 2,4-pentanedione, react quite well through a terminal carbanion site.^{32,41}

When there is a nucleophilic site on a side chain, ring closure through intramolecular $S_{RN}1$ reaction becomes a possibility. For example, the reaction shown in eq 7



occurs in 99% yield.⁴² Semmelhack and co-workers⁴² have explored such ring closure reactions, have recognized certain complications, and have employed such a reaction with spectacular success in the synthesis of cephalotaxine.⁴⁸

Solvents. Among several desirable characteristics in solvents for aromatic $S_{RN}1$ reactions, low reactivity with aryl radicals and low acidity (so as to be compatible with nucleophiles of high basicity) are prominent.⁴⁹ Liquid ammonia has been the solvent mainly used; it is advantageous because of its chemical characteristics, its ease of purification, and its ease of removal in work-up. Among other solvents that have been tried,⁴⁹ dimethyl sulfoxide is quite good and has seen some use, especially in quantitative studies.^{21,50}

Concerning the Reaction Mechanism

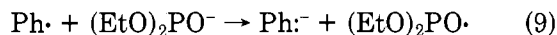
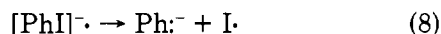
As mentioned, our early conviction that reactions of certain aryl iodides with amide ion occur in part by the $S_{RN}1$ mechanism arose from observations of inhibition by radical scavengers and stimulation by solvated electrons. Observations both of inhibition by radical or electron scavengers^{19,21,32-35,50} and of stimulation by solvated electrons^{16-18,27,36,48} have been made in numerous other cases.

The reaction of iodobenzene with diethyl phosphite ion in Me_2SO (eq 6) has been subjected to quantitative

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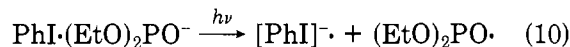
- (44) J. F. Bunnett and R. H. Weiss, "Organic Syntheses", John Wiley, New York, N.Y., in press.
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photochemical study.⁵⁰ Raw quantum yields as high as 50 were observed, and they constitute compelling evidence for a chain mechanism. The rate was observed to depend approximately on the 0.84 power of light intensity. That implies that termination or pretermination⁵¹ is mainly first order in a reactive propagating intermediate. Two conceivable pretermination steps first order in a propagating intermediate are shown in eq 8 and 9. These kinetically different



pretermination steps require kinetically different rate-limiting propagation steps, but a cancellation of concentration factors in one case causes both to call for the same overall kinetic expression.

The mechanism of photoinitiation is not known. An attractive possibility, compatible with available evidence⁵⁰ but not compelled by it, is that a charge-transfer complex of nucleophile with substrate undergoes electron transfer from one moiety to the other upon interaction with a photon, as for example in eq 10.



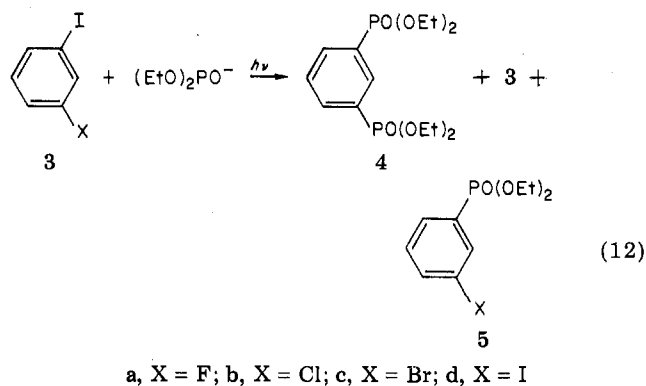
A kinetic study of the dark reactions of PhI and PhBr with pinacolone enolate ion (eq 11, with R = *t*-Bu) in PhX + CH₂=C(O⁻)R → PhCH₂C(O)R + X⁻ (11)

Me₂SO revealed several characteristics indicative of the S_{RN}1 mechanism, including inhibition by di-*tert*-butylnitroxide and *p*-dinitrobenzene and acceleration of bromide ion release from PhBr by adding PhI.²¹

Probably the strongest evidence for the mechanism is its capacity to account for several extraordinary phenomena now to be described. Accounting for them requires some adaptation or extension of the mechanism as proposed in 1966,^{3a,4} but no change in its essential features.

The Behavior of Dihalobenzenes. One might suppose, a priori, that one halogen would be substituted, and then the other, and that the questions to be answered would concern the substituent effects of the uninvolved halogen on the first substitution and of the nucleophile-derived moiety on the second. However, the situation is more sophisticated than that, for there is evidence that in some cases the involvement of the first halogen triggers the involvement of the second.

Consider the reaction of *m*-bromiodobenzene (3c) with diethyl phosphite ion in ammonia^{31,52-54} (eq 12). Upon interruption after 7-min irradiation, 60% of disubstitution product 4, 7% of monophosphonate ester 5c, and 28% of unreacted 3c were found.⁵³ It is striking that so little monosubstitution product was present in the company of so much disubstitution product and so much unreacted 3c. Such a condition might arise if substitution were stepwise and the conversion of 5c to 4 were much faster than of 3c to 5c. However, the



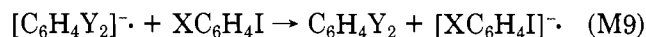
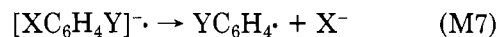
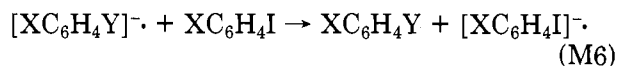
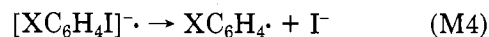
transformation of 5c to 4 was found to be slower than of 3c to 4.⁵³ It follows that 5c cannot be an intermediate on the main pathway from 3c to 4.⁵⁵

A similar experiment with similar result has been performed in respect to the photostimulated reaction of *m*-chloriodobenzene (3b) with thiophenoxide ion.⁴⁶ The outcome shows that disubstitution to form *m*-bis(phenylthio)benzene for the most part does not occur stepwise via *m*-chlorophenyl phenyl sulfide.

These results have huge mechanistic significance. If one were to approach de novo the question, for example, of how 3c reacts with (EtO)₂PO⁻ to form 4, considering every possible reaction mechanism, he might write down many mechanisms, some rational, some outlandish, and sagely he might recognize that others as yet not conceived might later join the list. Many of those mechanisms would involve 5c as an intermediate, and all of that sort must be rejected.

The S_{RN}1 mechanism provides, however, a straightforward interpretation. Let us rewrite the propagation sequence of Scheme I for the case of iodobenzene substituted with a second halogen, as in Scheme III. Steps M4, M5, and M6 are of exactly the same character as the three steps of Scheme I. Step M7 provides for the possible fragmentation of intermediate [XC₆H₄Y]^{·-} to expel X⁻, and is of the character of step M1. Step M8 is like step M2, and step M9 is an electron transfer like step M3.

Scheme III



Scheme III provides two alternative propagation cycles. One comprises steps M4, M5, and M6 and effects replacement of iodine but not of halogen X. The other comprises steps M4, M5, M7, M8, and M9, and results in replacement of both halogens. Which cycle prevails depends on the relative rates of steps M6 and M7.

(51) Pretermination refers to a step which does not actually destroy radicals, but rather converts reactive, propagating radicals into lethargic radicals which are essentially unable to do anything but terminate.

(52) J. F. Bunnett and R. P. Traber, *J. Org. Chem.*, **43**, 1867 (1978).

(53) J. F. Bunnett and S. J. Shafer, *J. Org. Chem.*, **43**, 1873 (1978).

(54) J. F. Bunnett and S. J. Shafer, *J. Org. Chem.*, **43**, 1877 (1978).

(55) These experiments do not exclude the possibility that 3c reacts stepwise, with bromine being replaced first, to form 5d which then is rapidly converted to 4. Inasmuch as PhI is about 1000 times more reactive than PhBr⁵² with (EtO)₂PO⁻, this possibility is remote.

The gross significance of Scheme III is that it provides for the conversion of $\text{XC}_6\text{H}_4\text{I}$ to disubstitution product $\text{C}_6\text{H}_4\text{Y}_2$ without the intermediacy of monosubstitution product $\text{XC}_6\text{H}_4\text{Y}$. Instead, it proposes the radical anion of the latter, $[\text{XC}_6\text{H}_4\text{Y}]^-$, to be an intermediate.

Scheme III enables interpretation of a number of remarkable observations concerning photostimulated reactions of haloiodobenzenes with the nucleophiles $(\text{EtO})_2\text{PO}^-$ and PhS^- , as now described.

(a) Diiodobenzenes and bromiodobenzenes give predominantly or exclusively disubstitution, but fluoroiodobenzenes undergo replacement only of fluorine.^{31,52} *Interpretation:* The order of frangibility of C-X bonds in aryl halide radical anions is known to be: C-I > C-Br > C-Cl > C-F. Compared to step M6, fragmentation step M7 is rapid when X is I or Br, but slow when X is F. Step M7 leads to disubstitution, and M6 to monosubstitution.

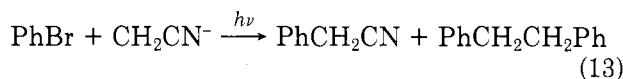
(b) *m*-Bromiodobenzene with $(\text{EtO})_2\text{PO}^-$ gives mainly disubstitution, but *m*-chloriodobenzene gives mainly monosubstitution.^{31,54} *Interpretation:* In crucial intermediate $[m\text{-XC}_6\text{H}_4\text{PO}(\text{OEt})_2]^-$, the C-X bond fragments (step M7) faster when X is Br than Cl. In consequence, step M7 predominates when X is Br but step M6 when X is Cl.

(c) With either *m*-bromo- or *m*-chloriodobenzene, disubstitution waxes and monosubstitution wanes as the substrate concentration is lowered.⁵⁴ *Interpretation:* The rate of bimolecular step M6 diminishes as the substrate becomes more dilute, but the rate of unimolecular step M7 is unaffected.

(d) *m*-Chloriodobenzene gives predominantly disubstitution with PhS^- but mainly monosubstitution with $(\text{EtO})_2\text{PO}^-$.^{31,46} *Interpretation:* The rate of fragmentation of a substituted aryl halide radical anion diminishes as the substituent is more strongly electron attracting. Of the two Y substituents in the $[m\text{-ClC}_6\text{H}_4\text{Y}]^-$ concerned, $-\text{PO}(\text{OEt})_2$ ($\sigma_p + 0.60$)⁵⁶ attracts electrons more strongly than does $-\text{SPh}$ ($\sigma_p + 0.08$).⁵⁷ and therefore step M7 is slower in the reaction of the phosphorus nucleophile. The change of substituent Y probably also affects step M6, but the results suggest that the substituent effect on M6 is of lesser magnitude.

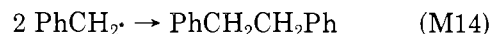
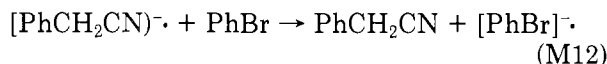
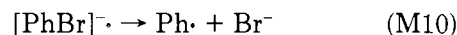
(e) Whereas *m*-chloriodobenzene with $(\text{EtO})_2\text{PO}^-$ gives principally monosubstitution,³¹ its para isomer gives mainly disubstitution.⁵² *Interpretation:* Measurements (especially by cyclic voltammetry) of rates of fragmentation of the radical anions of aryl halides substituted with electron-attracting groups show that para isomers fragment much faster than meta.^{6,7} For instance, the radical anion of *p*-bromobenzophenone fragments to bromide ion and aryl radical 250 times faster than does its meta isomer.⁶ Since $-\text{PO}(\text{OEt})_2$ is rather strongly electron attracting, step M7 is much faster in the reaction of *p*- than of *m*-chloriodobenzene.

Fragmentation of Radical-Anion Intermediates in the Nucleophile-Derived Moiety. The photostimulated reaction of bromobenzene with the cyanomethyl anion is sluggish and yields mainly 1,2-diphenylethane but also some phenylacetonitrile¹⁷ (eq 13). Formation of 1,2-diphenylethane is attributed to fragmentation of the phenylacetonitrile radical anion



as in step M13, Scheme IV, and dimerization of the resulting benzyl radicals (in step M14).

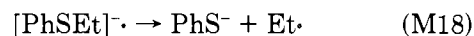
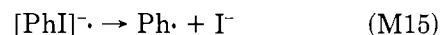
Scheme IV



The facile decyanation of phenylacetonitrile to toluene, through the action of potassium metal in ammonia,¹⁷ is independent evidence that step M13 occurs. Step M13 is a pretermination step,⁵¹ for the benzyl radicals that it forms do not react fast enough with cyanomethyl anion to perpetuate a propagation cycle. What they mainly do is to dimerize and terminate the chain, and hence the sluggishness of the reaction.

Although the photostimulated reaction of iodobenzene with PhS^- to form Ph_2S is rapid and efficient,³⁰ that with ethanethiolate ion is sluggish and affords a mixture of products: 30% PhSEt , 44% thiophenoxide ion, and 3% Ph_2S .⁴⁷ Formation of PhSEt is ascribed to the normal $\text{S}_{\text{RN}}1$ propagation sequence involving steps M15-M17, Scheme V, in this case. The appearance of PhS^- is attributed to fragmentation step M18, which is independently indicated by evidence of other sorts.⁴⁷ The PhS^- so formed undergoes further reaction with iodobenzene to form Ph_2S in small amount.

Scheme V



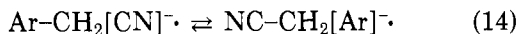
The fact that Ph_2S phenylates acetone enolate ion,^{15,19} apparently by the $\text{S}_{\text{RN}}1$ mechanism, suggests that radical anion $[\text{Ph}_2\text{S}]^- \cdot$ fragments into $\text{Ph} \cdot$ and PhS^- . Accordingly one might anticipate complications in $\text{S}_{\text{RN}}1$ reactions of aryl iodides with arenethiolate ions to form unsymmetrical diaryl sulfides. Thus, reaction of PhI with ArS^- (where $\text{Ar} \neq \text{Ph}$) would involve the combination step, $\text{Ph} \cdot + \text{ArS}^- \rightarrow [\text{PhSAr}]^- \cdot$, which might be followed by fragmentation to $\text{Ar} \cdot$ and PhS^- and ultimate formation both of Ph_2S and Ar_2S . An assiduous search in one case failed to reveal any such byproducts.⁴⁷ In this instance the potential fragmentation appears to be slower than electron transfer to continue the propagation sequence.

Rossi, de Rossi, and Lopez^{18,28} have shown that 1-chloronaphthalene undergoes photostimulated reactions with cyanomethyl anion and with 1-butanethiolate ion to give straightforward substitution products in high yield, without any evidence of fragmentation such as in step M13 (Scheme IV) or M18 (Scheme V). For reactions with cyanomethyl anion, they suggest an

(56) L. D. Freedman and H. H. Jaffé, *J. Am. Chem. Soc.*, **77**, 920 (1955).

(57) H. H. Szmant and G. Suld, *J. Am. Chem. Soc.*, **78**, 3400 (1956).

equilibrium between two isomeric structures for the intermediate radical anion,^{18,58} as in eq 14. The



symbolism is meant to indicate that the "extra" electron resides either in an antibonding (π^*) MO of the cyano group or in a π^* MO of the aryl group.

Molecular orbital calculations indicate that the structure $\text{ArCH}_2[\text{CN}]^{\cdot-}$ is energetically favored when Ar is phenyl but that $\text{NC-CH}_2[\text{Ar}]^{\cdot-}$ is preferred when Ar is α -naphthyl.⁵⁸ Rossi et al.^{18,28,58} propose that only $\text{ArCH}_2[\text{CN}]^{\cdot-}$ is able to fragment into ArCH_2^{\cdot} and CN^- . They recognize an alternative possibility, namely, that the whole radical anion, $[\text{ArCH}_2\text{CN}]^{\cdot-}$, is more stable when Ar is α -naphthyl rather than phenyl, and that in consequence fragmentation as in step M13, Scheme IV, is delayed long enough for electron transfer as in step M12 to occur. However, treatment of α -naphthylacetonitrile with potassium metal in ammonia failed to cause decyanation, but rather Birch reduction in the naphthalene ring, consistent with their favored hypothesis.¹⁸

The Argentine workers²⁸ have also shown that other ArX in which the lowest unoccupied molecular orbital of the aryl moiety is of lower energy than for benzene (e.g., 4-chlorobiphenyl, 2-chloropyridine, 4-chlorobenzophenone) undergo straightforward photostimulated reaction with cyanomethyl anion, affording ArCH_2CN in high yields.

Comparisons of Reactivity. Overall reactivity in an $S_{RN}1$ process is composite, being affected by the rates of initiation, propagation, and termination steps. One would prefer to know absolute rate constants for the component steps, but as yet no such data are available.

By means of competition experiments, the relative reactivities of pairs of halobenzenes with several reagents have been measured. Invariably the order of reactivity is: $\text{PhI} > \text{PhBr} > \text{PhCl} > \text{PhF}$. For photostimulated reactions with acetone enolate ion in ammonia, the reactivity ratios $\text{PhI}/\text{PhBr} = 8.3$, $\text{PhBr}/\text{PhCl} = 450$, and $\text{PhCl}/\text{PhF} = 29$ were obtained.⁴³ With pinacolone enolate ion in Me_2SO , the PhI/PhBr ratio is 6.²¹ The PhI/PhBr ratio in photostimulated reaction with $(\text{EtO})_2\text{PO}^-$ in ammonia is about 1000,⁵² and with diphenylphosphide ion about 300.⁴⁵ Thus the PhI/PhBr ratio is strongly dependent on the nucleophile.

If the chain is long, initiation and termination steps of whatever character have little effect on the relative reactivity of two competing substrates. When fragmentation step M1 is much faster than conceivable alternative pathways available to $[\text{PhX}]^{\cdot-}$, as may be the case with iodo- and bromobenzenes, selectivity between two substrates will be determined in electron-transfer step M3. The great variation in PhI/PhBr reactivity ratios must then be attributed to changing selectivity in step M3 as group -Y in $[\text{PhY}]^{\cdot-}$ is changed.

If step M1 is not the only pathway effectively available to $[\text{PhX}]^{\cdot-}$, other processes such as electron transfer back to PhY (reversing step M3) or to PhX' (the competing substrate) become significant, and reactivity in fragmentation step M1 will affect the PhX/PhX' reactivity ratio.

(58) R. A. Rossi, R. H. de Rossi, and A. F. Lopez, *J. Org. Chem.*, **41**, 3367 (1976).

The relative reactivities of aromatic systems have been studied by Wolfe and co-workers.^{34,35} In photostimulated reactions with acetone enolate ion, the reactivity orders 2-chloroquinoline > iodobenzene and 2-chloroquinoline > 2-bromopyridine > bromobenzene were found to obtain.

By performing a series of (dark) $S_{RN}1$ reactions of pinacolone enolate ion with mixtures of bromobenzene and substituted iodobenzenes, we were able to assess the competitive reactivity of the latter as affected by the substituents present.⁵⁹ The data gave an approximately linear Hammett $\rho\sigma$ plot with ρ about +0.6. In contrast, the reactivities of the same substituted iodobenzenes as measured separately (not in competition) showed a large substituent effect, ρ being about +6. Doubtless the remarkable difference in ρ values has to do with the contributions of initiation and termination steps to overall reactivity in separate reactions.

Autoinitiated Reactions. For those $S_{RN}1$ reactions that occur spontaneously in the dark, such as of amide ion with 5- or 6-iodopseudocumene² (Scheme II) or of pinacolone enolate ion with iodobenzene in Me_2SO ,²¹ the mechanism of initiation is unclear. A reasonable possibility³ is thermally activated electron transfer from nucleophile to substrate, as in eq 15.



The fact that unstimulated aromatic nucleophilic substitution can occur by the $S_{RN}1$ mechanism suggests that this mechanism may obtain for reactions long known. Recent work²² shows that the dark reaction of diphenylphosphide ion with aryl halides to form triarylphosphines (eq 16), known since 1963,⁶⁰ responds to probes of mechanism in a manner characteristic of the $S_{RN}1$ mechanism.



For determining which mechanism prevails in an aromatic nucleophilic substitution, the halogen mobility order is a criterion of some but limited value. In most S_{NAr} reactions,^{12,13} it is: $\text{ArF} \gg \text{ArCl} \sim \text{ArBr} \sim \text{ArI}$. The order for $S_{RN}1$ reactions, $\text{ArI} > \text{ArBr} > \text{ArCl} > \text{ArF}$, is unfortunately more or less shared with the aryne mechanism,⁶¹ certain S_{NAr} reactions (those in which expulsion of the nucleofuge is rate-limiting) and the double displacement mechanism indicated for reactions of organotin anions with aryl halides.⁶² Other criteria useful for recognizing $S_{RN}1$ reactions are inhibition by radical or electron scavengers, initiation effects, and entrainment effects.

Concluding Remarks

The tale that I have told starts with discovery that certain aromatic nucleophilic substitutions proceed by a novel mechanism not previously recognized for substitution at aromatic sites. It then tells how, emboldened by conviction that this mechanism would have wide validity, we found several new reactions, some of which have obvious value in synthesis. The saga tells

(59) R. G. Scamehorn and J. F. Bunnett, Abstracts, 4th IUPAC Conference on Physical Organic Chemistry, York, England, Sept 1978.

(60) A. M. Aguiar, H. J. Greenberg, and K. E. Rubenstein, *J. Org. Chem.*, **28**, 2091 (1963).

(61) J. F. Bunnett and F. J. Kearley, Jr., *J. Org. Chem.*, **36**, 184 (1971).

(62) K. R. Wursthorn, H. G. Kuivila, and G. F. Smith, *J. Am. Chem. Soc.*, **100**, 2779 (1978).

how diverse complications and reactivity effects encountered have served to define in part the rules that govern this new principle of aromatic substitution. By no means has every synthetic opportunity been captured or every troublemaking complication been vanquished. Many problems of mechanism remain unsettled, and some are probably yet unrecognized. The saga is uncompleted. Indeed, perhaps only the first few stanzas have yet been sung.

One still finds in current textbooks statements that unactivated aryl halides are unreactive with nucleophiles except under the strongly basic conditions

conducive to the aryne mechanism. My co-workers and I believe that the books need to be revised.

In this research I have been fortunate to have a group of able co-workers, some of them more the optimist willing to try the long shot, some more the pessimist ever seeking evidence to challenge theoretical hypotheses. Each has made characteristic contributions, and for all I am deeply appreciative. Financial support has been provided by the National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, the University of California, the Swiss Stiftung für Stipendien auf dem Gebiete der Chemie, and the Argentine Consejo Nacional de Investigaciones Científicas y Técnicas.

Structure and Stereochemistry in Metalloboron Cage Compounds

RUSSELL N. GRIMES

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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The remarkable ability of boron to form stable, covalently bonded cagelike molecules is by now a familiar fact to most chemists. In its own way, the study of boron cage compounds has emerged as a new kind of organic chemistry in which the main structural patterns (due to the presence of only three valence electrons in the boron atom) feature three-dimensional polyhedral clusters rather than chains and rings. Indeed, the capacity of boron to generate catenated, or self-bonded, molecular networks of considerable complexity is a property exhibited by no other element except carbon. Several decades of research on the boranes and their heteroatom-containing derivatives—carboranes, metalloboranes, metallocarboranes, thia- and phosphaboranes, and others—have produced an enormous proliferation of novel synthetic and structural chemistry, and spawned whole new fields of study. It is striking, therefore, to realize that there are still no discernible limits on the size, elemental composition, or geometry that can be adopted by these molecules. Certainly, the structures and reactions of the boron cage molecules have to a large extent been placed in a rational framework. Boron chemistry is no longer the jungle of disconnected facts it may have seemed at one time, nor is it remote from other areas of research; the recognition of close links between the boron cages and other kinds of clusters is a major development about which more will be said later.

Yet basic questions remain: Is there an upper boundary to polyhedral size? (Cages having 4 to 14 vertices inclusive are presently known.) How many different elements can coexist in a stable polyhedron,

and what extremes of atomic size and electronegativity can be tolerated? (Over 40 elements from main groups 2–6 and many transition metals in a variety of oxidation states have been incorporated into boron frameworks.) What limitations are there on the geometries that can be assumed by polyhedral cages, and on the coordination numbers and valence bond angles that may be adopted by individual atoms in these systems? One thinks here, by way of contrast, of the severe restrictions that govern the stereochemical role of carbon in organic compounds.

Perhaps surprisingly, these fundamental issues now present a more formidable challenge than was apparent several years ago. The fact is that the sophisticated techniques—synthetic, physical, and theoretical—which have been brought to bear on boron cage chemistry have opened up new, previously unsuspected avenues at a far greater rate than they have settled old problems. Though we might have expected the pace of discovery at some point to begin to abate, this has not occurred, and investigators continue to be confronted with reactions that were not supposed to happen and novel molecular structures that no one imagined to exist. These unexpected findings, of course, are of importance in continually reeducating us about the nature of cage and cluster compounds and about bonding and structure generally. Observations that support current theory can be useful, but those that force its extension and reshaping are more likely, in the long run, to advance our basic understanding of nature (which is a prime reason for studying exotic species such as the polyhedral boranes in the first place).

In this Account, following a brief discussion of structure, I will outline in a highly selective fashion some of the more significant twists and turns we and others have recently encountered on the trail of boron cage compounds, concentrating on problems with which my co-workers and I have been directly concerned. An

Russell N. Grimes was born in Meridian, Miss., in 1935, and raised in Pennsylvania. He received the B.S. degree from Lafayette College and the Ph.D. from the University of Minnesota. After postdoctoral research at Harvard University and University of California, Riverside, he joined the faculty at the University of Virginia, where he is Professor of Chemistry. His research interests include the synthesis and study of polyhedral cage and cluster compounds and elucidation of molecular structure by pulse Fourier transform NMR and X-ray crystallography.