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From Tars to Products: How To Disentangle the Reactions of Nitrobenzenes with Nucleophiles

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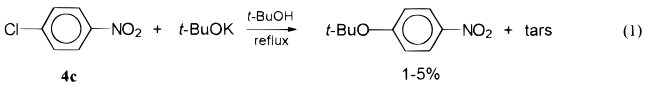
Introduction

Several years ago we asked a student to synthesize *p*-nitrophenyl *tert*-butyl ether according to the general procedure based on the reaction of activated aryl halides with alkoxide ions in the parent alcohol (eq 1). After



(1)

several attempts, which produced only minor amounts of the expected ether (1−5%) along with several other compounds, described at the time as "tars", the student abandoned organic chemistry for studies in electrochemistry, and we were left with the problem of explaining why the expected S_NAr reaction was not taking place.

A scrutiny of several alkoxide/alcohol pairs indeed revealed that nucleophilic substitution on *p*-chloronitrobenzene is efficient only with MeO^-/MeOH and EtO^-/EtOH, the reaction with other alkoxide/alcohol pairs giving little or none of the expected ether.[1] With 2-PrOK/2-PrOH, the expected 4-nitrophenyl isopropyl ether is obtained in small yield, along with numerous other products, including (see Chart 1) 4,4′-dichloroazoxybenzene (**7c**), 4-chloroaniline (**5c**), 4-nitrophenol (**4oh**), and 4,4′-dichloroazobenzene (**6c**).[2]

Thus, in contrast to the notion prevailing in textbooks and reference works, reaction of chloronitrobenzenes with alkoxides is of limited use for the synthesis of nitrophenyl ethers because of competing reduction. Since chloronitrobenzenes are commercially much more convenient starting materials than the corresponding fluorides and many nitrophenyl ethers are industrially important products (pharmaceuticals, pesticides, etc.), it is not surprising that an extensive bibliography is available, mostly as patents,[3] reporting "remedies" to prevent undesired reduction and promote nucleophilic substitution on substrates such as **4c**. Despite all this work, little information was available to guide the experimentalist wishing to obtain a specific product from such familiar and useful reagents.

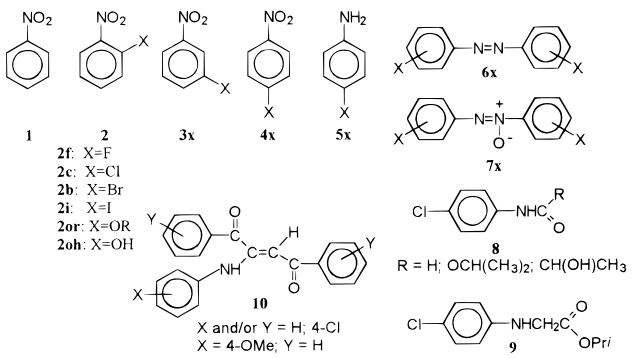
This Account describes our efforts to unravel the patterns of reaction of nitrobenzenes with anionic nucleophiles in protic solvents, particularly of halonitrobenzenes, for which the dichotomy substitution vs reduction exists. We have gained some understanding of the underlying complex reaction schemes and mechanisms and of the factors which, in different ways, affect reactivity in these systems. Through this knowledge, it is now possible to control reactivity in such a way as to promote one specific reaction and obtain the desired product with a good yield.

Reactions of Nitrobenzenes with Alkoxides

The reaction of *p*-chloronitrobenzene (**4c**) with alkaline 2-propanol turned out to be a very sensitive probe of reactivity. The effect of molecular oxygen on both rates and products is quite dramatic. While products of both substitution and reduction are generally obtained, only oxy-dechlorination to **4or** (R = 2-Pr, 40%) and **4oh** (12%) occurs, in a slow process ($t_{1/2}$ = 11 h), when oxygen is bubbled through the solution under otherwise typical conditions (75 °C and nucleophile in 10-fold excess). The decay of **4c** becomes much faster under oxygen-free conditions ($t_{1/2}$ = 15 min) and leads exclusively to products of nitro reduction.[2]

The investigation was extended to all twelve halonitrobenzenes.[4] *o*- and *p*-fluoronitrobenzene are highly

Chart 1[a]



[a] The identities of X substituents are, in general, represented as in the family of compounds **2**.

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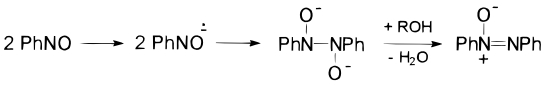
Scheme 1



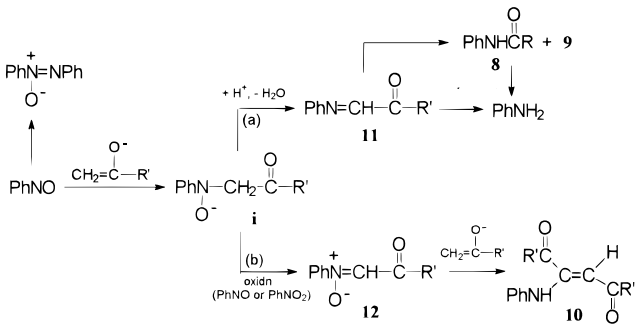
activated for the S_NAr reaction and undergo fast and quantitative alkoxydehalogenation, regardless of the presence of oxygen. *o*-Iodonitrobenzene, on the other hand, is quantitatively converted to nitrobenzene, as discussed later. Save for these three exceptions, all halonitrobenzenes undergo reduction of the nitro group. In oxygen-free alkaline 2-propanol, nitro reduction is, in general, the kinetically favored process. The reaction is strongly inhibited by oxygen, an efficient oxidant of nitrobenzene radical anions ($k = 10^5-10^7$ M^{-1} s^{-1}),[5] a result consistent with the generally accepted notion that reduction in alkaline protic solutions proceeds via the intermediacy of the substrate radical anion.[6] Such species can be viewed as the first stage of reduction in a very complex redox cascade, in which nitrosobenzene is the key intermediate. Control experiments showed that, under our experimental conditions, nitrosobenzenes are more reactive than their nitro precursors and are quantitatively converted to the corresponding azoxybenzenes, likely via one-electron reduction and dimerization, as proposed in 1965 by Russell and Geels (Scheme 1).[7]

Interestingly, when the nitrosobenzene is formed during reduction of the corresponding nitrobenzene, azoxybenzene is the major but not the only product obtained. Thus, reaction of **4c** yielded **7c** (57%), **5c** (12%), **6c** (6%), and amino derivatives **8** (R = H (6%), R = $OCH(CH_3)_2$ (1%), and R = $CH(OH)CH_3$ (1%)), and **9** (1%).[8] The origin of such products was somewhat intriguing. It was excluded, by means of control experiments, that any could derive from reaction of the conceivable precursors azoxybenzene, azobenzene, and phenyl-*N*-hydroxylamine.[8] A clue came from the observation that reduction of nitroarenes by the alkoxide/alcohol systems is sustained by oxidation of the solvent, which, in the case of 2-propanol, produces acetone and water (eq 2). Acetone was, indeed, found among the reaction products.

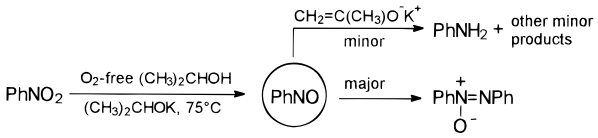
$$PhNO_2 + (CH_3)_2CHOH \xrightarrow{(CH_3)_2CHOK} PhNO + (CH_3)_2C{=}O + H_2O \quad (2)$$

Nitrosobenzenes are known to add carbanions to form covalent anionic adducts.[9] In our case, the nitrosobenzene can be trapped by acetone enolate (adduct **i** in Scheme 2, R′ = CH_3), a step in competition with reductive dimerization to azoxybenzene. It was, indeed, found that additions of water and acetone, or any enolizable ketone, such as acetophenone (Scheme 2, R′ = Ph), resulted in increased aniline production, via condensation to **i**, followed by water elimination and hydrolysis (route a in Scheme 2). Following these observations, experimental conditions were optimized to obtain anilines in very good yield (80−98%).[10] With added enolate ion but in the absence of water, on the other hand, the γ-diketone **10** (Chart 1) is obtained with yields up to 80%, via oxidation

Scheme 2



Scheme 3



of **i** to a nitrone (**12**) and further enolate addition (route b in Scheme 2).[11] Support for Scheme 2 came from studies of the reactivity of postulated key intermediates, the ketoimino (**11**) and the nitrone (**12**) derivatives.

Reduction of nitrobenzenes with 2-PrOK in oxygen-free 2-PrOH can, therefore, be usefully summarized as shown in Scheme 3. The first stage, reduction to the nitroso compound, is the slow one, but it is the second which, through competing reactions of such intermediates, determines the reaction products.

It is possible to block effectively all this complex redox chemistry by bubbling oxygen into the solution. Under these conditions, the slower substitution process becomes competitive for substrates such as **4c**. The reaction is, however, of no practical use for the synthesis of **4or** (R = 2-Pr), since the conversion is slow and the yield unsatisfactory. The reaction efficiency is greatly improved, however, by use of tetra-alkylammonium ions or alkali ion complexing agents, such as crown ethers, glymes, and polyethylene glycols.[1] This enhancement was attributed to an increase of the alkoxide ion nucleophilicity due to loss of aggregation with the counterion,[1] a well-understood and exploited ion-pairing phenomenon.

It was found, indeed, that reaction of **4c** with different alkoxides (ROK) in the parent alcohols (ROH) shows, upon complexation of K^+ by 18-crown-6, rate enhancements which parallel the trend of the RO^-K^+ ion association constants in ROH.[12] Since these kinetic determinations were carried out in oxygen-free solutions, it was remarkable and unexpected to find[12] that the quantitative conversion of **4c** into **4or** (R = 2-Pr) observed in the presence of 18-crown-6-complexed K^+/2-propoxide proceeded at a rate which was lower ($k = 0.7 \times 10^{-3}$ s^{-1}) than that of the reduction process ($k = 1.09 \times 10^{-3}$ s^{-1}) taking place under exactly the same conditions but without 18-crown-6.[4] The addition of crown ethers must, therefore, bring about not only an increase in the rate of substitution but also a decrease in that of reduction. This conclusion was verified experimentally. Figure 1a reports kinetic data obtained in a set of experiments with nitrobenzene, for

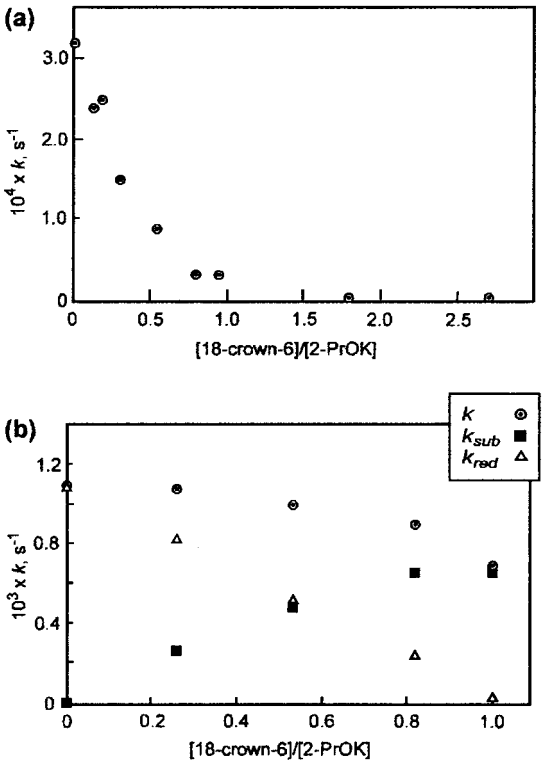


FIGURE 1. Ion-pairing effects for reactions of 2-PrOK (0.265 M) in oxygen-free 2-PrOH at 75 °C with (a) nitrobenzene (0.025 M) (the rate of reduction decreases with increasing concentration of 18-crown-6)[6] and (b) *p*-chloronitrobenzene (0.02 M) (partitioning based on product data shows that, as the concentration of 18-crown-6 increases, the rate of reduction decreases while the rate of substitution increases; consequently, the observed overall rate does not change much with the concentration of 18-crown-6).[4]

which reduction is the only viable route, run all under identical (standard oxygen-free) conditions except for the amount of 18-crown-6 used. The observed rate constant ($k = k_{red}$) decreases with increasing crown concentration, down to a plateau, reached when sufficient crown is present to complex the K^+ ion quantitatively.[6] An analogous set of experiments was conducted with *p*-chloronitrobenzene (Figure 1b). Coupled product and rate measurements showed that, while the observed rate constant (k) does not change much with the concentration of 18-crown-6, the product composition changes from 100% reduction (no 18-crown-6 present) to ca. 100% substitution (enough 18-crown-6 present to complex K^+ quantitatively). The trends observed for the derived rate constants for reduction (k_{red}) and substitution (k_{sub}) nicely illustrate the opposite kinetic effects on the two competing processes due to release of ion-pairing interactions: acceleration of nucleophilic substitution and inhibition of nitro reduction.[4] If one were to rely only on the rates of decay of *p*-chloronitrobenzene in 2-PrOK in 2-PrOH, the wrong conclusion would have been reached, that cation complexation has no significant effect on the reaction.

These experiments brought to attention a specific aspect of the reduction of nitrobenzenes by alkali in alcohols which had, until then, remained undetected, i.e., the role of the cation, which, with a localized and

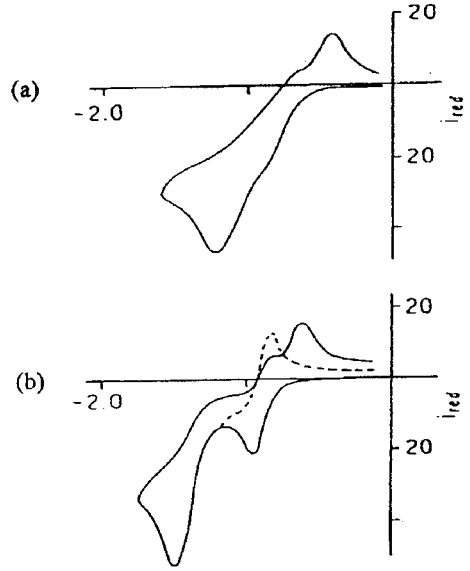
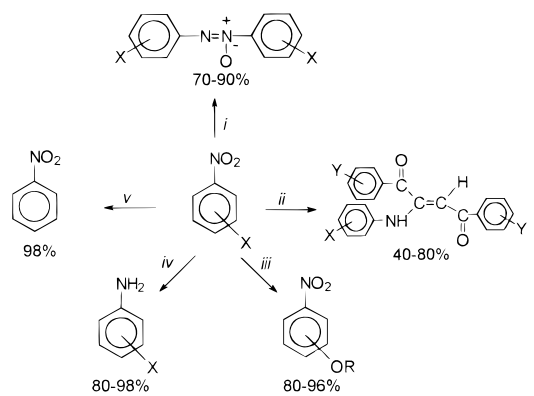


FIGURE 2. CV curves for reduction of *p*-chloronitrobenzene in oxygen-free 2-PrOH in the presence of M^+SCN^- (0.08 M): (a) $M^+ = K^+$ and (b) $M^+ = K^+$/18-crown-6.[13]

Scheme 4[a]



[a] Conditions: (i) KOH in MeOH/toluene (1:3), reflux; use of higher alcohols activates the route to aniline.[10] (ii) $YC_6H_4COCH_3$ and 2-PrOK in 2-PrOH, reflux; water is to be excluded to avoid hydrolysis of key intermediates.[11] (iii) Bu_4NBr (or crown ethers, Carbowax, or other cation-complexing agents) and KOH in ROH, heat.[1] (iv) CH_3COPh in 50% aqueous KOH/2-PrOH (1:5), reflux.[10] (v) 2-PrOK in O_2-free 2-PrOH, 75 °C (only for X = 2-I).[4]

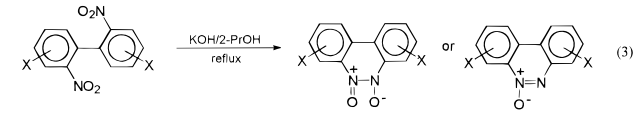
unshielded charge, favors the reaction, likely by stabilizing some crucial anionic intermediate through ion pairing. Obviously, such characteristic behavior is of great advantage for practical applications and for understanding the mechanism of such reactions.

An important clue about the steps leading from nitro- to nitrosobenzenes is offered by the remarkable differences observed in the cyclic voltammetric profiles for reduction of **4c** in neutral 2-propanol, recorded in the presence of alkali metal cations (K^+, Na^+, Li^+) or of n-Bu_4N^+ and 18-crown-6-complexed K^+ or Na^+.[13] While an overall four-electron reduction irreversible peak is observed for the former, a two-wave trace is recorded for the latter, consisting of a first reversible one-electron peak followed by an irreversible three-electron peak (Figure 2). Notably, the separation into two peaks is due to a shift of the second reduction wave toward more negative poten-

tials and was therefore attributed, in the sequence $ArNO_2 \rightarrow ArNO_2^{-\bullet} \rightarrow ArNO_2^{2-} \rightarrow ArNO$, to a greater difficulty of the nitrobenzene radical anion to accommodate a second charge in the absence of specific solvation by the counterion.[13] Such a conclusion, coupled with the inhibition of the chemical reduction with ROK/ROH observed with complexed alkali ions, points to the involvement of dianion species, formed by one-electron reduction of the radical anion, in the rate-determining step of the reduction process, as discussed in the final section of this Account.

The experiments described above and the knowledge acquired from them led, as practical rewards, to the development of procedures for the efficient synthesis of specific targets, as outlined in Scheme 4.

The mechanistic concepts governing the substitution vs reduction competition were also successfully applied to the synthesis of substituted benzo[*c*]cinnoline *N*-oxides and *N*,*N*-dioxides via intramolecular reductive cyclization of 2,2′-dinitrobiphenyls (eq 3).[14]



(3)

X = H; 5,5′-Cl_2; 4,4′-$(CH_3)_2$; 4,4′-$(CF_3)_2$; 5,5′-$(2\text{-PrO})_2$ (55-77%)

Reactions of Nitrobenzenes with Other Anions

Relevant results of the extension of this research to different nucleophiles are presented and discussed in the following section.

Reactions with Thiol Anions

Thiol anions are weaker bases than the corresponding alkoxides but usually are more reactive as nucleophiles and reducing agents. All thiol anions examined (RSNa, R = Me, Et, 2-Pr, *t*-Bu, Ph) react with *o*- and *p*-chloronitrobenzene in oxygen-free 2-propanol at 40 °C to give the product of *ipso* substitution in quantitative yield.[15] The only exception is *t*-BuS^-, for which the yields of the substitution product are lower (68−78%) due to competing redox processes. The mechanistic features of these substitution reactions are all consistent with the scheme of the S_NAr process. In particular, no significant effects are observed in the presence of dissolved oxygen. The order of reactivity within the series of the investigated nucleophiles, $MeS^- > EtS^- > 2\text{-}PrS^- > PhS^- > t\text{-}BuS^-$, is opposite, as far as the alkanethiol anions are concerned, to the order of basicity. Steric effects were then considered since reactivity diminishes with increasing bulkiness of the nucleophile. However, the relative reactivities of *o*- and *p*-chloronitrobenzene (k_{ortho}/k_{para}) toward MeS^- ($k_{ortho}/k_{para} = 0.71$; k_{para} is usually larger than k_{ortho} in reactions of halonitrobenzenes with anionic nucleophiles) and toward *t*-BuS^- ($k_{ortho}/k_{para} = 2.3$) suggest that steric effects in the transition state are scarcely dependent on the bulkiness of group R in the attacking nucleophile. These data, as well as kinetic results obtained with "naked" anions (RS^-/18-crown-6-complexed Na^+), are consistent with the alternative explanation that, due to the inductive effect of R, the charge is more concentrated on the heteroatom in the case of *t*-BuS^- than of MeS^-. Consequently, a greater degree of association with the cation and stronger ion-pairing effects are to be expected for the former anion.[15] More efficient ion pairing in RS^-Na^+ reduces the nucleophilic reactivity of the thiol anion. Results consistent with this interpretation were obtained in a recent study based on ^{23}Na NMR analysis of various NaY (Y = RS, RO, etc.) in 2-propanol solution.[16]

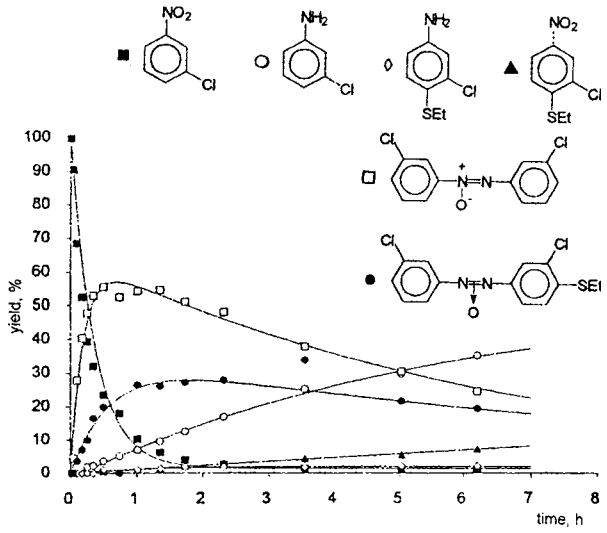


FIGURE 3. Time-dependent product distribution for reduction of *m*-chloronitrobenzene (0.0094 M) with EtSNa (0.094 M) in oxygen-free 2-propanol at 40 °C.[19]

In contrast with the behavior of 2-propoxide, all thiol anions examined promote nucleophilic substitution rather than redox processes. Their expected superiority as reductants manifests itself, however, in the reactions with nitrobenzenes which are not suited for nucleophilic substitution. Thus, *m*-chloronitrobenzene is reduced by 2-PrSNa at 40 °C[15] at approximately the same rate as by 2-PrOK at 75 °C.[4] Interestingly, the same reactivity order is observed for reduction of *m*-chloronitrobenzene by the alkanethiol anions as for substitution of *p*-chloronitrobenzene. Benzenethiol anion, however, proved inert in the reduction of the nitro group, even at temperatures higher than 40 °C, in contrast with its good reactivity in the S_NAr reaction. Thus, *m*-chloronitrobenzene was recovered quantitatively after treatment with a 10-fold excess of PhSNa at 75 °C over several hours.

In reactions with *m*-chloronitrobenzene, thiol anions give not only higher rates but also more complex product mixtures than observed with alkoxide ions. Considerably larger fractions of anilines are formed as well as numerous and rather abundant products of nitro reduction which have also undergone thioalkoxylation at the para position (Figure 3). Moreover, the product distribution depends on the specific thiol anion used and also on the reaction time, as is apparent in the example of Figure 3, which shows that reactions take place well after complete decay of the primary nitrobenzene reagent.

The high yields in anilines, obtained from these reactions, could be due to fast coupling between a nitrosobenzene intermediate and a thiol anion. The reaction of nitrosobenzenes with thiols is important in biological systems and is responsible for certain damaging processes leading to methemoglobinemia, carcinogenesis, or mutagenesis.[17] By means of in situ ^{1}H NMR analysis of the reaction between a nitrosobenzene and a thiol in 2-propanol, we obtained spectroscopic evidence for a covalent adduct, an *N*-hydroxysulfenamide (−N(OH)−S−), formed in a rapid and quantitative initial coupling step of the two reagents.[18] It was also possible to follow the slower decay of such an intermediate along a complex sequence of steps, producing eventually aniline and azoxybenzene in relative proportions and at a rate which depends on the reagents' initial molar ratio.[18] However, in no instance could we obtain aniline from the reaction of a nitrosobenzene with the anions of the same thiols, azoxybenzene being, in this case, the only and quantitative product.[19]

An alternative route to aniline was therefore considered, following the observations that the concentration of such product(s) increases well after complete conversion of the precursor nitrobenzene and corresponds to a decay of azoxybenzenes (Figure 3). We found, indeed, that azoxybenzenes, which are stable in 2-PrOK/2-PrOH at 75 °C, undergo reduction to the corresponding anilines by treatment with alkylthiol anions in the same solvent at 40 °C.[20] Interestingly, this new reaction, which is presently being further investigated, does not take place with benzenethiol anion.

Reactions of Nitrobenzenes with C Anions

Nitrobenzenes have commonly been used as oxidants of carbanions, and it is generally accepted that such oxidations proceed via single-electron transfer.[21,22] Alongside these fundamental studies, focused on the reactivity and fate of carbanions,[21] important research developed reactions with carbanions or their equivalents to achieve alkylation of nitrobenzenes.[23,24]

The S_NAr reaction of 9-R-fluorenyl anions with *p*-halonitrobenzenes in DMSO was studied by Bordwell and Hughes.[25] We extended the investigation to the ortho isomers and found that the reactivity depends drastically on the halogen and, to some extent, on the R substituent on C9 of the fluorene precursor. Thus, while with *o*-fluoronitrobenzene the product of *ipso* substitution is obtained in quantitative yield (R = Me, Et), the same product amounts only to 50% yield in the case of *o*-chloronitrobenzene and to 3−5% for the bromo and iodo compounds.[19]

It was of interest to test the relative ability of one such carbanion to induce reduction and substitution on suitable substrates under the same conditions used for the alkoxide and thiol anion reactions. It was found that, in 2-propanol, reaction of 9-ethylfluorenyl anion with *m*-chloronitrobenzene yields the azoxy compound **7c** (3,3′-dichloroazoxybenzene, 73% isolated yield), whereas reaction with *p*-chloronitrobenzene yields both the products of reduction (**7c**, 4,4′-dichloroazoxybenzene, 40% isolated yield) and of *ipso* substitution (40% isolated yield).[19] The product of oxidative coupling of the carbanion, the 9,9′-bifluorene derivative, also formed in these reactions. With regard to the reduction vs substitution competition for our model substrate, *p*-chloronitrobenzene, the behavior of this carbanion is intermediate between that of alkoxide ions (exclusive reduction) and of thiol anions (exclusive substitution). Another interesting observation concerns the higher yield of azoxy compound obtained in the reaction of *m*-chloronitrobenzene with respect to that in the alkoxide-promoted reaction. It would thus appear that such bulky carbanions are less effective than the acetone enol anion in trapping the nitroso intermediate.

Occurrence of Nitrobenzenes Radical Anions and Their Role as Reaction Intermediates in These Systems

The chemistry of nitrobenzenes in basic solutions is the chemistry of the anionic species derived from them: Jackson−Meisenheimer σ-complexes (monoanions but, in special cases, also di- and polyanions, resulting from multiple nucleophilic additions), radical anions, and dianions, the latter formed in what, at least formally, amounts to transfer of two electrons. All such species have been the object of thorough mechanistic and structural investigations.[26] The introduction of a nitro group on a benzene ring greatly enhances the ease of formation and the stability of the corresponding arene radical anion by reducing the energy of the LUMO. While the radical anions of plain aryl halides, ArX (X = Cl, Br, I), readily fragment to aryl radicals and X^-, and are therefore typical substrates for the $S_{RN}1$ reaction, the nitro-substituted analogues generally do not. Such species undergo further reduction to the corresponding dianions, which, under suitable experimental conditions, are sufficiently long-lived to be detected and studied by traditional electrochemical techniques. Thus, nitro-substituted chloro-, bromo-, and iodobenzenes undergo two consecutive reversible electronation steps in liquid ammonia.[27] For mononitrobenzenes, both Meisenheimer monoanions and radical anions often coexist in the same basic solution. Clearly, this variety of potential intermediates is the cause of the complexity of the final product mixture often obtained from such reactions.

We detected the radical anion of nitrobenzenes **1**, **3c**, and **4c** by in situ EPR analysis of solutions of such compounds reacting with 2-PrOK in oxygen-free 2-propanol at 75 °C. Interestingly, more intense signals were observed in the presence of 18-crown-6-complexed K^+.[6]

Nitroaryl halide radical anions are also produced in oxygen-free 2-propanol solutions of aliphatic thiol anions, even at room temperature.[19] Figure 4 reports ^{1}H NMR spectra of a solution of *m*-chloronitrobenzene and 2-PrSNa in 2-PrOH-d_8 recorded with and without oxygen. The dramatic signal broadening observed when oxygen is removed from the solution is attributed to rapid degenerate electron transfer between neutral *m*-chloronitroben-

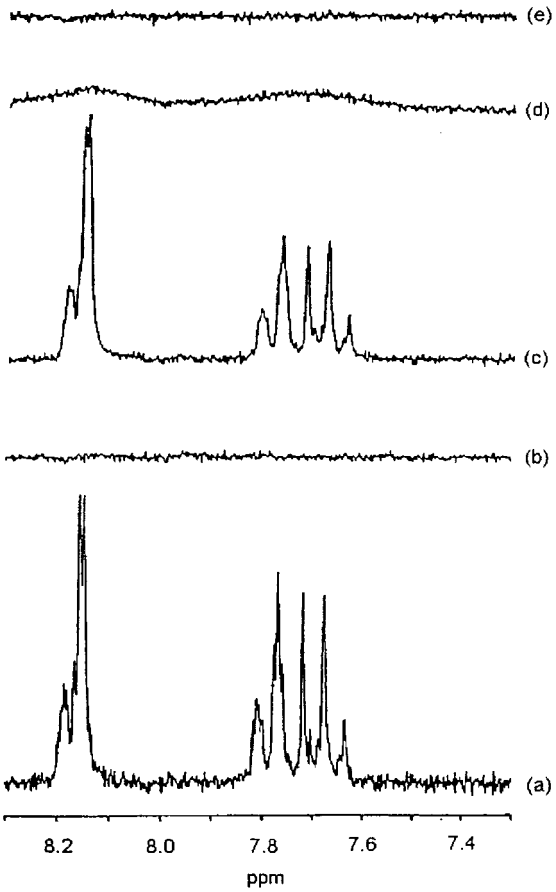
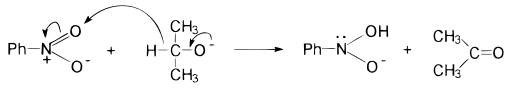


FIGURE 4. ^{1}H NMR spectra of a 2-propanol solution of *m*-chloronitrobenzene (a) in oxygen-free 2-propanol at 40 °C; (b) after addition of 10-fold EtSNa; (c) after bubbling oxygen; (d) after bubbling argon to remove oxygen; and (e) after complete removal of oxygen.[19]

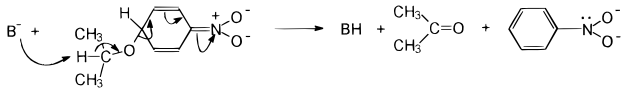
zene and its radical anion. The original signal is resumed after bubbling oxygen through the solution: the whole cycle can be repeated many times.[19] These observations are consistent with the occurrence of radical anions and their quenching by molecular oxygen. The same behavior was observed also with *p*-chloronitrobenzene. Interestingly, while both *p*- and *m*-chloronitrobenzene behave in the same way as far as the NMR analysis is concerned, the response of their reactivity to the introduction of oxygen is quite different. Thus, reaction of *p*-chloronitrobenzene with 2-PrSNa proceeds unaffected by the presence of oxygen to give the product of nucleophilic substitution, whereas that of *m*-chloronitrobenzene, giving products of nitro reduction, is inhibited by oxygen (50% conversion in 50 min reaction time in oxygen-free solution vs <10% conversion in 120 min in the presence of oxygen).[19] In our opinion, these observations provide a clear-cut criterion for understanding the role of radical anions in these systems, namely that of "spectators" in the former case (nucleophilic substitution) and of reaction intermediates in the latter (reduction).

In conclusion, molecular oxygen has no effect on nucleophilic aromatic substitution by RS^- on *o*- and *p*-halonitrobenzenes, regardless of whether the substrate radical anion is formed (R = alkyl) or not (R = Ph), showing that radical anion formation and S_NAr can be two

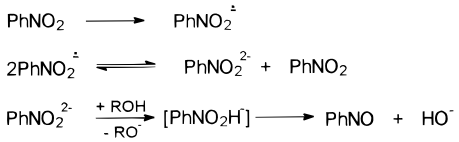
Scheme 5



Scheme 6



Scheme 7



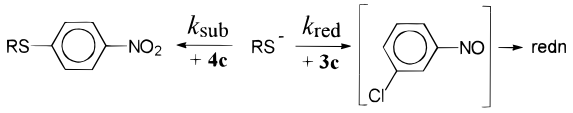
parallel, independent processes. These conclusions are perhaps relevant to recent proposals to reconsider the established two-electron S_NAr mechanism within the framework of the theory of electron transfer.[28,29,30] The matter of such mechanistic distinctions is, however, beyond the concern of the present Account, which deals with the differentiation between radical and nonradical processes.

A Scheme for the Nitro to Nitroso Reduction

A couple of attractively simple mechanisms for the anion-induced reduction of nitro- to nitrosobenzenes are sketched in Schemes 5 and 6, based, respectively, on hydride transfer to an oxygen of the nitro group and on base-induced decomposition of an initially formed Jackson–Meisenheimer intermediate to the nitrobenzene dianion and acetone. Both mechanisms are, however, dismissed since they do not account for the following evidence: (i) the reaction is inhibited by crown ethers (the activity of the alkoxide ion, both as a nucleophile and as a base, increases in the presence of ion-pairing-disrupting agents);[31] (ii) the reaction is inhibited by O_2; (iii) the substrate radical anion is an intermediate *along* the reaction path (the inhibition by O_2 is due to quenching of such a key intermediate); (iv) the formation of side products of reduction, in which oxidative nucleophilic substitution of hydrogen has occurred. Additional evidence against both Schemes 5 and 6 comes from the observation that also *t*-BuOK in *tert*-butyl alcohol brings about reduction of nitrobenzenes with the same general features of the 2-PrOK/2-PrOH reaction, although more slowly.[2]

We have shown that reduction of the substrate radical anion to the corresponding dianion is rate-limiting in these processes. Therefore, one reasonable reduction route to arrive at the nitrosobenzene compound involves bimolecular dismutation of the radical anion to nitrobenzene and dianion, followed by fast proton transfer and HO^- elimination. Such a decay was observed for the nitrobenzene radical anion generated photochemically in alkaline methanol[32] and radiolytically in water containing some 2-propanol.[33] The overall sequence is shown, for the parent compound, in Scheme 7.

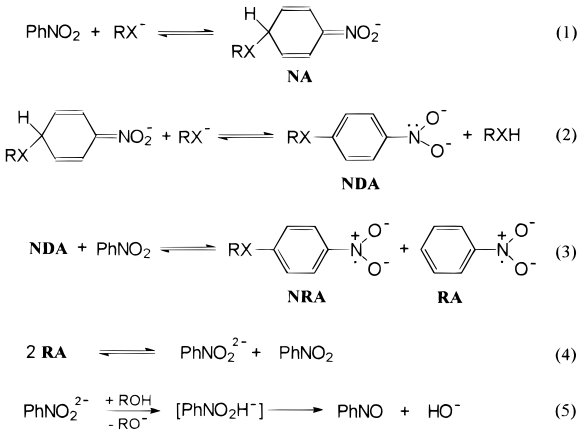
Scheme 8



	MeS^-	EtS^-	2-PrS^-	*t*-BuS^-	PhS^-
$\underline{k}_{sub}$[a]	68.1	30.0	15.1	(1.00)[b]	9.94
$\underline{k}_{red}$[a]	54.3	14.3	9.78	(1.00)[c]	-[d]

[a]Relative rate constants, $\underline{k} = k(RS^-)/k(t\text{-}BuS^-)$, where k are the observed rate constants for reaction of tenfold RSNa (0.094 M) with **4c** (k_{sub}) or **3c** (k_{red}) in 2-PrOH at 40°C. [b]$k_{sub} = 1.6\times10^{-5}$ s^{-1}.[15] [c]$k_{red} = 2.3\times10^{-5}$ s^{-1}.[19] [d]Too slow to be measured.

Scheme 9

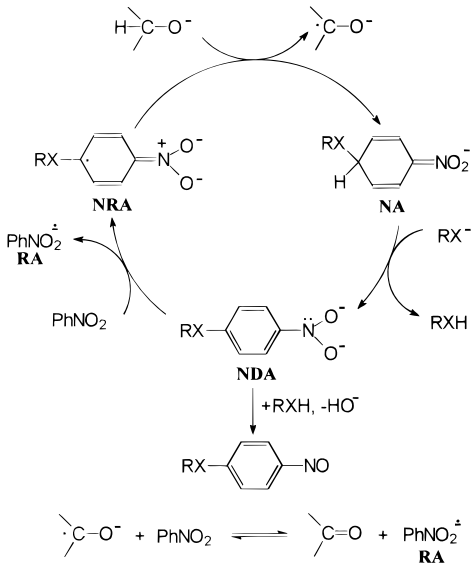


How are the radical anions of nitrobenzenes formed in our systems? Electron transfer from the nucleophile is unlikely since the $\Delta G°$ estimated for such a step is >60, ca. 44, and ca. 32 kcal mol^{-1} for RO^-, EtS^-, and PhS^-, respectively.[34] Remarkably, according to such estimates, electron transfer should be most favorable from benzenethiol anion, in the reactions of which no experimental evidence was obtained for the nitrocompound radical anion.[19] In contrast, electron transfer from carbanions was classified as feasible.[34]

Reactivity data of thiol anions offer a clue. The rates of nitro reduction of *m*-chloronitrobenzene[19] and of the S_NAr substitution on *p*-chloronitrobenzene[15] decrease in a parallel way as R is changed from Me to Et to 2-Pr to *t*-Bu. A striking point of rupture in this trend is observed for PhS^-, which has a reactivity similar to that of 2-PrS^- in the S_NAr reaction but is ineffective in promoting reduction (Scheme 8).

Noting that there is a considerable difference in the proton basicity of aliphatic and aromatic thiol anions (the former are stronger bases by at least 4 pK_a units),[35] a reasonable proposal for the origin of the substrate radical anion (abbreviated as **RA**) is shown, again for the parent compound nitrobenzene, in steps 1−3 of Scheme 9.[36] The proposal, which follows the mechanism of Guthrie and Nutter for the formation of nitrobenzene radical anion in the reaction of nitrobenzene with *t*-BuOK in THF,[37] is consistent with the now established role of dianions in

Scheme 10

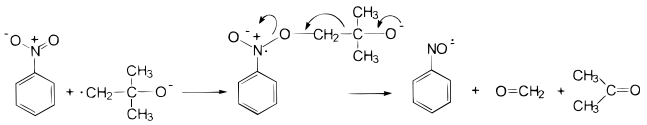


the key steps of many base-induced processes of nitrobenzenes.[38,39] According to Scheme 9, the **RA** is formed via electron transfer from dianion **NDA** (**N** refers to the presence of the nucleophile on the ring), which is produced via nucleophilic addition and deprotonation in the first two steps of the reaction. Reduction of **RA** to nitrosobenzene proceeds, then, according to steps 4 and 5, as already shown in Scheme 7.

Questions which are not addressed in Scheme 9 concern the fate of **NRA**, the ring-substituted radical anion formed, along with **RA**, in the electron-transfer step 3, as well as the origin of acetone and of products of reduction in which oxidative nucleophilic substitution of hydrogen has occurred. Such issues are dealt with in Scheme 10. Let us consider first the products of ring substitution. These form in highly variable amounts, depending on the specific reagents and experimental conditions. They account for a considerable fraction of the overall product balance obtained from reactions with thiol anions, as seen in the example of Figure 3: ethylthio-substituted dichloroazoxybenzenes and aniline make up for ca. 30% of the starting material in this case. Analogous products were also isolated, although in much smaller amounts, from the reaction of *m*-chloronitrobenzene with methoxide ion in MeOH/toluene.[36] All such "side" products are easily accounted for by considering decay of dianion **NDA** according to the familiar sequence of protonation and elimination of HO^-, which we believe represents the main reduction channel of the nitro group in these systems (Scheme 7). As shown in Scheme 10, such decay is in competition with the crucial electron-transfer reaction (step 3 in Scheme 9), which forms two radical anions, **RA** and **NRA**.

The format of Scheme 10 is meant to emphasize conceivable propagation steps which account for the production of acetone and for the fate of **NRA**. The key step is one which recycles **NRA** as the Jackson−Meisenheimer adduct **NA**, by way of H-abstraction from the

Scheme 11



alkoxide ion. The other product of such a step, the ketyl radical anion, is capable of producing **RA** via the electron-transfer step included at the bottom of Scheme 10, in agreement with the strongly reducing properties[40,41] of ionized α-hydroxyalkyl radicals, •C(RR′)O⁻ (R, R′ = H, CH_3), which reduce nitrobenzenes via fast direct outer-sphere electron transfer.[41]

We note that reaction of **RA** by the same H-abstraction and deprotonation route as that proposed for **NRA** in Scheme 10 leads to dianion **DA**. Although such a path cannot be excluded for the reduction of the substrate, it cannot be the main reaction channel because it does not fit the ion-pairing effects observed both in the electrochemical and in the chemical reduction of nitrobenzenes, which support the decay of **RA** via electron transfer to **DA**.

In the case of tertiary alkoxides, like *t*-BuO⁻, which, as mentioned earlier, brings about reduction of nitrobenzenes in the parent alcohol,[2] the H atom abstraction step of Scheme 10 could involve either one of the C−H bonds or the O−H bond. In the first case, $•CH_2C(CH_3)_2O^-$ and/or its conjugate acid, $•CH_2C(CH_3)_2OH$ (pK_a > 13.5),[42] would be formed. While the latter β-hydroxyalkyl radical is a very weak one-electron-transfer reducing agent,[43] not much is known about its ionized form. One reasonable expectation is that either radical should be able to reduce nitrobenzene via an addition/elimination mechanism (Scheme 11), the first step of which, addition to one of the nitro group oxygens, is consistent with the known reactivity of a few α-hydroxyalkyl radicals, •C(RR′)OH.[41] The suggested decay of the intermediate adduct accounts for the observed production, in the reaction of 4-chloronitrobenzene with *t*-BuOK in *t*-BuOH, of acetone and of small amounts of 4-methoxynitrobenzene,[44] which can be attributed to reaction of methoxide ion formed in the disproportionation of formaldehyde.

The less likely abstraction of hydrogen from the O−H group would produce the *tert*-butoxy radical, which is known to decay to acetone via $•CH_3$ elimination.[45]

In summary, Schemes 9 and 10 offer a collection of chemical steps which, to extents depending on the specific reaction partners and experimental conditions, may occur in sequence and/or in competition to bring about the nucleophile-induced reduction of the nitro group. Specifically, the schemes account for all the available experimental observations, in particular for (1) lack of reactivity of benzenethiol anion, too weak a base to generate dianion **NDA** in sufficient concentration to initiate the reduction process, (2) the ion-pairing phenomena, and (3) the formation of side products of reduction in which oxidative nucleophilic substitution of hydrogen has occurred.

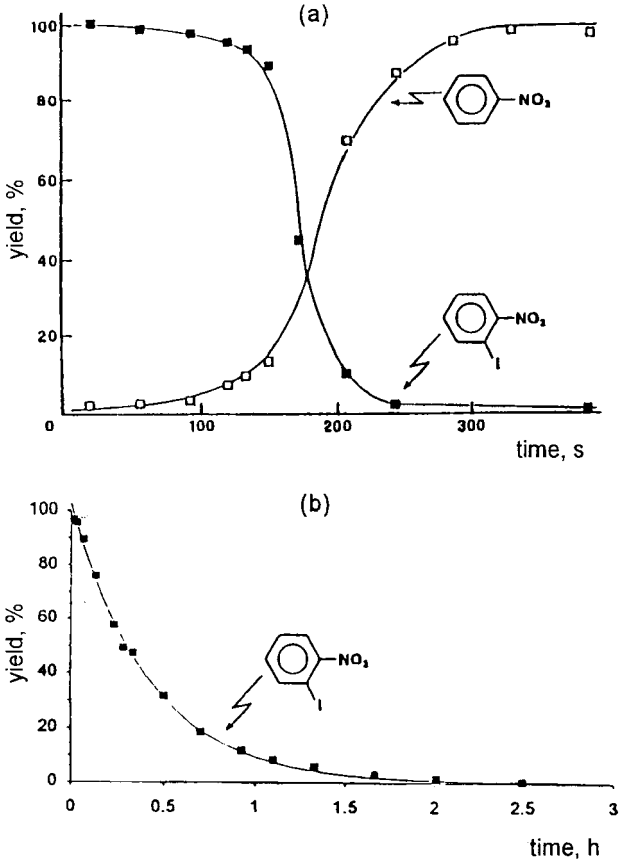


FIGURE 5. Decay of *o*-iodonitrobenzene due to reaction in oxygen-free 2-propanol with 10-fold (a) 2-PrOK at 75 °C[4] and (b) 2-PrSNa at 40 °C.[48]

The Peculiar Reactivity of *o*-Iodonitrobenzene

With all nucleophiles we have used, *o*-iodonitrobenzene displays a peculiar reactivity, resulting in reduction of the carbon−halogen bond to form nitrobenzene. With 2-propoxide[4] and with the 9-fluorenyl carbanions,[19] hydrodehalogenation was also observed, although to a smaller extent, also with *o*-bromo- and, to an even smaller extent, with *o*-chloronitrobenzene. Operation of the established radical chain mechanism for hydro-deiodination,[46] which involves, as the first step in the propagation cycle, the fragmentation of the substrate radical anion to I⁻ and the *o*-nitrophenyl radical, is consistent with the characteristic concentration vs time plots (Figure 5a) and with the known high rate of fragmentation of *o*-iodonitrobenzene radical anion (up to 5 orders of magnitude greater than that of its meta and para isomers) due to steric hindrance, which forces the nitro group out of the plane of the ring and reduces the energy gap between the π* and σ* orbitals.[47] When the reaction was conducted in 2-propanol-OD, the recovered product, nitrobenzene, had no D-incorporation, consistent with the intermediacy of the *o*-nitrophenyl radical.[48]

Quite different responses were obtained from the reaction with thiol anions.[48] Concentration vs time plots (Figure 5b) are simple exponential decays, and reactions

in 2-propanol-OD produce nitrobenzene of isotopic composition $C_6H_4DNO_2$, corresponding to 100% deuterium incorporation, thus excluding the intermediacy of *o*-nitrophenyl radicals. The results rather point to the involvement of a carbanion-like intermediate formed via attack of the nucleophile on iodine in a "halophilic" type reaction.[48]

From the results just described follows the somewhat unexpected conclusion that thiol anions display nonradical reactivity under conditions that, with the 2-propoxide ion, lead to reduction processes via radical intermediates. They also provide a remarkable example of the same product being obtained from the same precursor in the same solvent by two independent and well-characterized routes, one radical[4] and one nonradical,[48] depending on the nucleophile used.

Summary and Conclusions

The study of the reactions of halonitrobenzenes with nucleophiles in 2-propanol has disclosed the following processes and clarified their mechanisms:

(i) nitro group reduction;

(ii) S_NAr substitution of halogen by the nucleophile;

(iii) reduction of the carbon−halogen bond via radical anion fragmentation (limited to *o*-iodo- and, to a lesser extent, *o*-bromo- and *o*-chloronitrobenzene); and

(iv) reduction of the C−I bond via thiol anion attack on halogen (limited to *o*-iodonitrobenzene).

While reactions (iii) and (iv) are limited in scope, nitro group reduction and nucleophilic substitution are competing pathways for *o*- and *p*-halonitrobenzenes. Based on the available data, a comparison can be drawn for O, S, and C anions reacting with *p*-chloronitrobenzene: nitro reduction prevails with the first, and nucleophilic substitution with the second, while, with the third, the two processes are about equally efficient. The results with the alkoxide ions are particularly interesting, since these are common reactions. Since nitro reduction generally prevails in these systems, the common identification of *o*- and *p*-halonitrobenzenes as *halides* activated for nucleophilic substitution should, perhaps, be reconsidered to grant the nitro group its role as the actual reaction center.

Radical anions are generally formed in these systems but do not necessarily participate as intermediates along the main reaction path. The reaction of *o*-, *m*-, and *p*-chloronitrobenzene with alkanethiol anions provides a striking case: while NMR evidence for the substrate radical anion was found in all three cases, quenching of such species by oxygen had no effect on the reaction of the ortho and para isomers (nucleophilic substitution) but strongly inhibited the reaction of the meta isomer (nitro reduction via radical paths).

Radical anions undergo further reduction to the corresponding dianions, which then proceed to the nitroso intermediates and final products. Such a crucial reduction step is favored by strong ion pairing with the counterion, as occurs in solvents of low dielectric constant and in the absence of cation-complexing agents. Release of ion-pairing interactions has, therefore, opposite effects on nucleophilic aromatic substitution (rate increases) and nitro reduction (rate decreases). From a practical point of view, this is a fortunate situation which can be usefully exploited to promote either nitro reduction or substitution. Reduction of the nitro group can lead, in turn, depending on the reaction conditions, to different products in synthetically useful yields.

Finally, a comment seems appropriate on the situation, encountered more than once in our research, in which conclusions based exclusively on either kinetic analysis (e.g., the opposing kinetic effects due to ion pairing on competing reduction and substitution) or product analysis (e.g., the reactions of *o*-iodonitrobenzene with RO^- and RS^-) would have led to grossly incorrect interpretations of the experimental data. In fact, such examples could prove useful in teaching the necessity, fundamental in science, to base our knowledge and rationalization of facts on as many as possible complementary data. "Do not make verifiable assumptions", reads a framed embroidered poster in the office of the founder of this Journal.

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