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Understanding Reactivity Patterns of the Dialkylaniline Radical Cation

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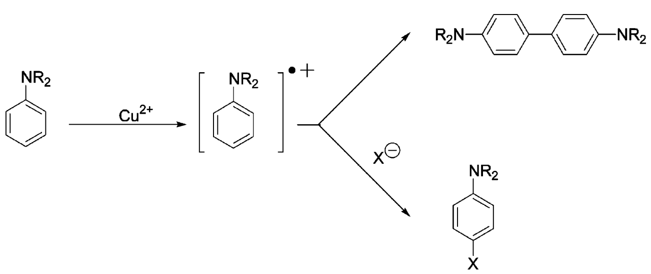

N,*N*-Dimethylaniline and *N*,*N*-diethylaniline react with Cu^{2+} to form the corresponding amine radical cations. The radical cations were characterized by their absorption spectra. In the absence of any nucleophiles, the radical cations dimerize to give tetraalkylbenzidines, and this reaction can be monitored by absorption spectroscopy. In the presence of nucleophiles such as $Cl^{\ominus}$, $Br^{\ominus}$, or $SCN^{\ominus}$, the radical cations undergo nucleophilic substitution to give *para*-substituted dialkylanilines in good yields.

The generation and study of radical cation intermediates has gained considerable interest in the last two decades.[1−9] Although radical cations can undergo a variety of reactions, such as bond cleavage, ring closure, deprotonation, isomerization, nucleophilic attack, and reactions with neutral reagents, the chemistry of radical cations is not as well developed compared to the chemistry of radicals or cations. Radical cations are considered to be interesting but synthetically ineffectual intermediates. The problem generally is associated with the techniques available for the generation and study of these intermediates. Radical cations are most generally prepared by photoinduced electron transfer (PET) in solution or electrochemical electron transfer at an electrode surface.[10−12] PET reactions generally require elaborate experimental set up for preparing and monitoring the follow up reactions of the generated radical cations. The short lifetimes of the generated radical cation in certain cases make these approaches less attractive. The electrochemical method suffers from the disadvantage that the radical cations are formed in very high concentrations at the electrode surface, leading to their dimerization. This often hampers the reactions of the radical cations with other substrates. Although long-lived radical cations can be generated within zeolite cavities, monitoring reactions of radical cations inside zeolites are rarely reported and often times difficult to achieve.[13]

We have recently introduced a very simple and effective method for the generation of aromatic amine radical cations.[14] The reaction involves mixing of the aromatic amine with 1 equiv of $Cu(ClO_4)_2$ in acetonitrile solution. The amine radical cation is generated as a result of single electron transfer from the amine to Cu^{2+} as shown in eq 1.

$$\text{Amine} + Cu^{2+} \rightarrow \text{Amine}^{+\bullet} + Cu^{+} \qquad (1)$$

We proposed that aromatic amines with oxidation potential less than 1.0 V (vs SCE) are capable of forming radical cations by this mechanism. In this paper, we show that this method can be effectively explored for generating aromatic amine radical cations and studying their reactivity patterns. Taking *N*,*N*-dimethylaniline (DMA) and *N*,*N*-diethylaniline (DEA) as examples, we show that this reaction can be used for synthetic applications, as well.

Addition of $Cu(ClO_4)_2$ to a solution of DMA resulted in the disappearance of the absorption due to DMA at <300 nm and formation of a new band at 470 nm.[14] On the basis of the literature[15] and also our own experiments,[14] the 470 nm band was unambiguously assigned to the DMA radical cation ($DMA^{\bullet+}$). The absorption at 470 nm is not very stable and gradually decreases in intensity and changes in to a structured absorption band (Figure 1A). This is associated with the formation of a highly structured absorption band above 800 nm. On the basis of the literature, this spectrum with structured absorptions around 470 and 1000 nm is assigned to the tetramethylbenzidine radical cation ($TMB^{\bullet+}$).[16] (In a separate experiment, this cation radical was generated by treating TMB with 1 equiv of $Cu(ClO_4)_2$ in acetonitrile. The UV spectrum obtained in this case was identical to that presented in Figure 1A(j).) Under the experimental conditions, $TMB^{\bullet+}$ was found to be stable for several hours but can be decomposed upon addition of a base such as triethylamine (TEA) or potassium

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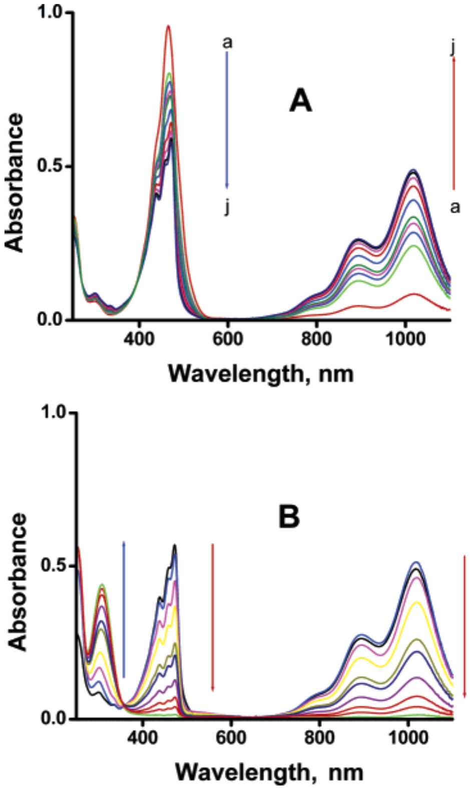

FIGURE 1. (A) Time-dependent changes observed in the absorption spectrum of a DMA/Cu(ClO$_4$)$_2$ mixture. Spectra a−d were recorded at 1 min intervals, and e−j were recorded at 5 min intervals. (B) Effect of addition of increasing amounts of TEA to solution in spectrum 1A-(j) above.

carbonate. Figure 1B shows the disappearance of TMB$^{•+}$ as a result of TEA addition. The new band formed around 300 nm is due to tetramethylbenzidine (confirmed by product isolation and recording spectrum of isolated product). A solution of DEA in acetonitrile also exhibited identical behavior as shown in Figure 1 in the presence of 1 equiv of Cu(ClO$_4$)$_2$. The new compound formed in this case was identified as tetraethylbenzidine (TEB).

Scheme 1 summarizes the observations made in Figure 1. Figure 1A suggests that transformation of dialkylanilines (PhNR$_2$) to the tetraalkylbenzidines does not involve any stable observable intermediates. This transformation, however, has to involve dimerization, deprotonation, and electron donation as shown in Scheme 2 (for DMA).

Presence of a clear isosbestic point in Figure 1A suggests that the dimerization to form the dihydrotetramethylbenzidine dication is the slowest step in Scheme 2. In general, radical cations and dications are highly acidic compared to neutral molecules, and hence the second step in Scheme 2 is expected to be very fast. The TMB thus formed is a better electron donor (E_{ox} = 0.32 V vs SCE) than DMA (E_{ox} = 0.81 V vs SCE).[17] Hence a very fast electron exchange reaction between the two takes place, leading to the formation of the TMB cation radical. If Cu^{2+} is present in excess, electron transfer from TMB to Cu^{2+} can also occur, leading to the formation of TMB$^{•+}$.

Anodic oxidation of DMA to TMB$^{•+}$ was studied previously in aqueous and nonaqueous solutions.[18,19] In these studies, attempts were made to detect DMA$^{•+}$ using fast cyclic voltammetry and optical spectrophotometry. These attempts were not successful, and it was concluded that DMA$^{•+}$ is very unstable and undergoes dimerization by a mechanism similar to that shown in Scheme 2. Under our experimental conditions, DMA$^{•+}$ and DEA$^{•+}$ were reasonably stable and could be characterized by UV−vis spectroscopy. We also show here that the dialkylaniline radical cation thus generated can lead to synthetically useful reactions. Some examples are shown in Table 1. As shown in Table 1, the radical cation produced dimerizes to give benzidine derivatives in 83−86% yield. When a nucleophilic reagent is present, the radical cation undergoes nucleophilic substitution to give the *para*-substituted products in good yields. See Supporting Information for experimental details and product characterization.

Benzidine derivatives have received much interest recently because of their applications in light-emitting diodes, field-effect transistors, organic solar cells, and photoconductors.[20−26] Oxidation of dialkylanilines to radical cations and their subsequent dimerization to benzidine derivatives has been achieved earlier with several reagents, including Cu^{2+}.[27−32] Jiang et al., for example, reported the oxidative coupling of dialkylanilines in 62−85% yield using CuBr (1 equiv)/H$_2$O$_2$ (10 equiv).[27] Oxidative couplings using TiCl$_4$ (1.5 equiv),[28] ceric(IV)ammonium nitrate (2 equiv),[29] and organic oxidants such as 1,8-bis-(diphenylmethylium)naphthalenediyl dication (1 equiv)[30] are recently reported. Most of these methods claim the intermediacy of radical cations. The existence of radical cations is not proved in any of these cases. The method presented here appears to be better in terms of the yield, simplicity, and ease of workup procedure. Most dialkylanilines have oxidation potentials less than 0.9 V (vs SCE), and hence the reaction is expected to be general for this class of compounds.

Under appropriate conditions, dialkylaniline radical cations can be trapped using nucleophiles to give ring substitution products in good yields as shown in Table 1. All these reactions take place at room temperature, and special precautions, such as inert atmosphere or dry solvents, are not required (detailed reaction conditions, NMR, and GC−MS traces are given in the Supporting Information). As is seen from Table 1, different types

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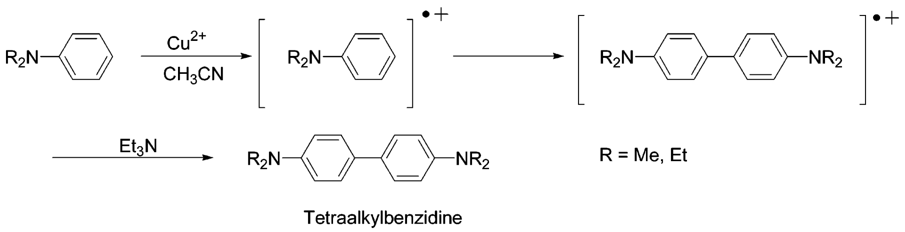
SCHEME 1



SCHEME 2

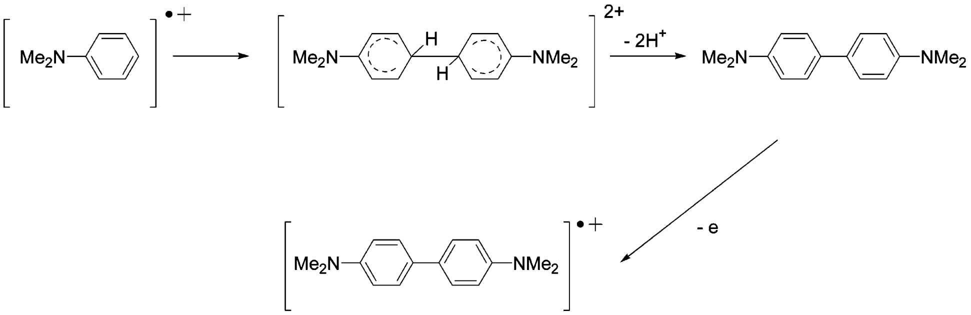
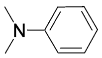
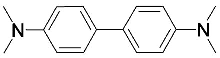
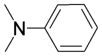
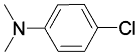
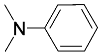
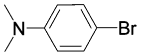
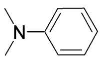
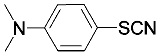
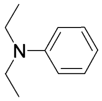
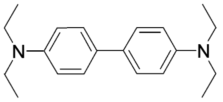
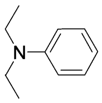
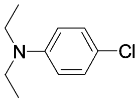
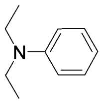
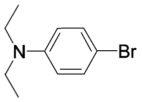
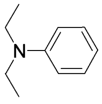
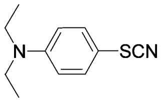


TABLE 1. Products and Yields in Cu^{2+}-Initiated Reactions of *N*,*N*-Dialkylanilines

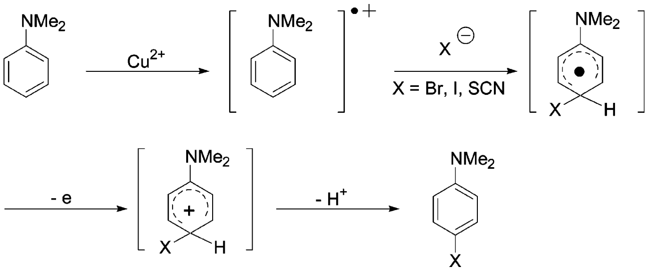
entry	substrate	reagents	product	yield (%)
1		Cu(ClO$_4$)$_2$		83
2		CuCl$_2$		52
3		(nBu)$_4$NBr, Cu(ClO$_4$)$_2$		86
4		NaSCN, Cu(ClO$_4$)$_2$		82
5		Cu(ClO$_4$)$_2$		86
6		CuCl$_2$		58
7		(nBu)$_4$NBr, Cu(ClO$_4$)$_2$		88
8		NaSCN, Cu(ClO$_4$)$_2$		85

of nucleophiles can be used, and the limiting factor here appears to be the solubility of the nucleophilic reagent in acetonitrile solution.

A possible mechanism for the formation of the substitution products is given in Scheme 3. The PhNR$_2^{\bullet+}$ formed as a result of electron transfer to Cu^{2+} is immediately trapped by the nucleophile to form the radical, which gives away an electron to form a cationic species. The electron can be transferred to PhNR$_2^{\bullet+}$ or to Cu^{2+} (if present in excess). The cationic species subsequently undergoes deprotonation to give the product. Attempts are being made to extend the scope of this reaction.

Although amine radical cations are well-known, nucleophilic substitution reactions involving these species have attracted little attention. Chlorination of DMA using acetyl chloride and

SCHEME 3



catalyzed by ceric ammonium nitrate was reported recently,[33] and this reaction might have involved DMA$^{\bullet +}$. Mechanistic details, however, are not discussed in the paper. It is to be mentioned that nucleophilic substitution reactions of cyanide and methoxide ions were attempted earlier on electrolytically generated DMA$^{\bullet +}$.[34,35] Substitution of these ions, however, occurred at the methyl group, and yields were very low. Formation of these products was explained using a mechanism which involved strong adsorption of the amine radical cation on to the positive electrode. The basic reaction conditions assist in removing a proton from the radical cation. This is followed by loss of a second electron to the electrode to give $Ph-N(CH_3)-CH_2^+$, which undergoes reaction with cyanide or methoxide ions. Adsorption on to the electrode and basic conditions are required for this mechanism to operate. The amine radical cation is only a transient intermediate in the electrolytic reaction, and the actual species reacting with the nucleophile is a cation. The mechanism in Scheme 3 is different from the electrolytic reactions in that the second electron transfer and deprotonation occur after the attack of the nucleophile.

In conclusion, we have generated radical cations of DMA and DEA by mixing with Cu^{2+} in acetonitrile solution and followed their reaction pathways using absorption spectroscopy. We have also explored the synthetic utility of this reaction. Oyama and co-workers have recently developed the technique of electron transfer stopped flow (ETSF) to generate and study the reactivity of amine radical cations.[36−38] This technique involves the use of electrochemically generated stable radical cations, such as the tris(*p*-bromophenyl)amine radical cation, to generate radical cations of amines with lower oxidation potentials. The present method of mixing the amine with Cu^{2+} salt seems to be much more efficient and simple.

Experimental Section

Representative Procedure for Benzidine Synthesis: Synthesis of *N,N,N′,N′*-Tetramethylbenzidine. A solution of copper(II) perchlorate hexahydrate (5.5 g, 15 mmol) in CH_3CN (10 mL) was added to a solution of *N,N*-dimethylaniline (1.2 g, 10 mmol) in CH_3CN (10 mL) over a period of 30 min at 25 °C, and the mixture was stirred for 10 h. Solid K_2CO_3 (4.0 g) was added, and stirring continued for 0.5 h. Filtered and the solids were washed twice with $CHCl_3$. The combined organic extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue so obtained was recrystallized from petroleum ether. Yield of pure product was 1.0 g (83%), mp 195−196 °C (reported mp 196 °C). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.6 (d, 4 H), 6.9 (d, 4 H), 3.1 (s, 12 H).

Representative Procedure for Substitution Reaction. Synthesis of 4-Bromo-*N,N*-dimethylaniline. *N,N*-Dimethylaniline (121 mg, 1 mmol) and tetrabutylammonium bromide (640 mg, 2 mmol) were dissolved in CH_3CN (30 mL). A solution of copper(II) perchlorate hexahydrate (740 mg, 2 mmol) in CH_3CN (10 mL) was added, and the mixture was stirred for 0.5 h at room temperature. Solid K_2CO_3 (1.0 g) was added, and stirring continued for 10 min. The reaction mixture was filtered, and the solids were washed twice with $CHCl_3$. The organic fractions were combined and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was taken in petroleum ether. This was filtered through a small alumina column and crystallized from the same solvent. Yield of pure product was 172 mg (86%), mp 54−55 °C (reported mp 55 °C). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.2 (d, 2 H), 6.5 (d, 2 H), 2.9 (s, 6 H).

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Supporting Information Available: Details of synthesis and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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