Mechanistic Insights into Substituent Effects on Reactivity of 2-(Methoxymethyl)benzene-1,4-diamine

AARON D. BAILEY,¹ GUIRU ZHANG,¹ BRYAN P. MURPHY²

¹Coty Inc, Cincinnati, OH, 45237

²Coty Inc, Blue Ash, OH, 45241

Received 7 April 2017; revised 2 July 2017; accepted 2 July 2017 DOI 10.1002/kin.21110

Published online in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: In the series of benzene-1,4-diamines (*p*-phenylenediamines) investigated, 2-(methoxymethyl)benzene-1,4-diamine (2-methoxymethyl-*p*-phenylenediamine) is the most slowly oxidized, with removal of the first electron being rate determining. This electronwithdrawing methoxymethyl group also drove a faster coupling step with 3-aminophenol (*m*-aminophenol) than for the analogs with electron-donating groups. However, the series parent, benzene-1,4-diamine, exhibited the fastest coupling step. Since both N(1) and N(4) of the primary intermediates react with *m*-aminophenol, it seems that steric hindrance by the 2-substituents slows the overall rate. When 3-amino-2,6-dimethylphenol is the coupler, the kinetics are biphasic. Nonproductive adducts are formed reversibly with all the primary intermediates by *ipso* attack at C(6). For 2-(methoxymethyl)benzene-1,4-diamine, formation of this nonproductive adduct is favored more than for the other compounds in the series, in what seems to be a kinetically rather than thermodynamically controlled process. This slows the overall rate of color formation. © 2017 Wiley Periodicals, Inc. Int J Chem Kinet 1–14, 2017

© 2017 Wiley Periodicals, Inc.

INTRODUCTION

Oxidative hair colorants have been popular for well over a hundred years. This technology requires that small, colorless molecules combine, generally mediated by H_2O_2 , to produce color.

Correspodence to: Bryan P. Murphy; e-mail: bpm8@aol.com. Present Addresses: Aaron D. Bailey, ANGUS Chemical Co., Buffalo Grove, IL 60089.

Supporting Information is available in the online issue at www.wileyonlinelibrary.com.



Scheme 1 Representative reaction of a 1 and 4, in which only the dimeric indo dye product is possible [1,2]. Nitrogen N(1) is ortho to the carbon to which R^1 is bonded, and N(4) is para to N(1).

In this process, primary intermediates such as benzene-1,4-diamines (*p*-phenylenediamines) and 4aminophenols (*p*-aminophenols) are oxidized to *p*benzoquinonedi- or monoimines, respectively. Subsequent electrophilic attack on couplers such as 3-aminophenols (*m*-aminophenols), benzene-1,3diamines (*m*-phenylenediamines), and resorcinols yield diphenylamines (leuco dyes), which are oxidized rapidly to form the final indo dye (azomethine). For example, Scheme 1 shows simplified coupling chemistry between benzene-1,4-diamine (1) and the blocked coupler, 5-amino-2-methylphenol (4).

Recently, advances to the chemistry and performance of benzene-1,4-diamine analogs have included addition of substituents to the aromatic ring of benzene-1,4-diamines and have made the dye-forming reaction pathway potentially more complex than what is pictured in Scheme 1. These advances have occurred because some of the more popular primary intermediates such as 1 and 2-methylbenzene-1,4-diamine (p-toluenediamine; 7) have come under increased regulatory scrutiny over the past few decades. However, the haircolor industry has been successful in replacing materials of concern over the past 40 years in its drive for improved performance and safety in hair dye chemistry. For example, we have recently developed and commercialized 2-(methoxymethyl)benzene-1,4diamine (8) as a primary intermediate that replaces 1 and 7 and that offers reduced allergenic potential [3,4].



In addition to improving the toxicological properties of benzene-1,4-diamines, substituents on primary intermediates, and also couplers, are used to fine-tune properties such as color, reactivity, solubility, and intensity of the resultant indo dyes. For example, addition of electron-donating or electron-withdrawing groups to the primary intermediate or the coupler can be used to manipulate the rates and extents of reaction. For the 1,3-disubstituted benzenes that are common couplers, blocking potential reaction sites also affects rates and limits the possibilities of the dyes that can be formed [1,2,5].

Determination of rates of individual steps to form an indo dye is difficult when unblocked couplers are used. For example, the complexity of the coupling of **1** with resorcinol has most recently been demonstrated by Bailey et al. [6]. Therefore, when studying the reactions of primary intermediates and couplers, it is common practice to block sites in the coupler so study of the first coupling reaction, i.e. when no oligomerization occurs, is more straightforward. Additionally, when studying mechanisms of oxidation and dye formation, use of potassium ferricyanide is a well-accepted approach [7,8]. This simplifies the kinetics by making the rate of oxidation much more rapid than the rate of coupling, thus allowing a more informative analysis of the coupling kinetics. Since our goal was to understand the effect of the methoxymethyl group on both rates of oxidation and coupling, we adopted these approaches, with one exception: We did also study the parent coupler (**4**) for comparison.

The above-mentioned understanding of dye products, rates of reaction, mechanisms of formation, and competitive kinetics with other oxidation dye intermediate pairs informs both the shade development work required to commercialize new haircolor products that use these materials, and also the design of next-generation dye intermediates. However, as new dye oxidation dye precursors have been introduced recently [9–11], the kinetics and mechanisms of dye formation from these materials have not been studied as extensively as for previous materials, as in the work of Corbett, Brown, Tong, and others, particularly for the primary intermediates. Recently, though, Mohr-Hautavoine et al. have published important information on the use and the comparative color delivery properties of 8 relative to 7, another commercial analog [12].

In general, the color from the indo dyes formed from $\mathbf{8}$ was slightly redder than the color from those formed from $\mathbf{7}$. Our interest was to understand the mechanistic drivers of their results in hair dyeing and to determine whether the same properties that shifted the color would also result in a change in rate or mechanism of color formation from $\mathbf{8}$.

EXPERIMENTAL

Materials

Benzene-1,4-diamine (*p*-phenylenediamine; 1) and 3aminophenol (*m*-aminophenol; 11) were purchased from Jos. H. Lowenstein and Sons, NY, NY, USA, and were sublimed prior to use. All other commercial chemicals were acquired from Sigma-Aldrich, St. Louis, MO, USA, and were used as received. Water refers to deionized water. 2-Methylbenzene-1,4-diamine sulfate salt, 2-(methoxymethyl)benzene-1,4-diamine, 3-amino-2,6-dimethylphenol, and 2propylbenzene-1,4-diamine dihydrochloride salt and were generously supplied by Dr. John Gardlik of Procter & Gamble, Cincinnati, OH, USA. Compressed gases were provided by Wright Brothers, Inc, Montgomery, OH, USA. Buffer refers to the corresponding phosphate buffer adjusted to pH 7.9, 9.25, 9.45, or 10.3, and I = 0.2 M with KCl. The buffer preparation details can be found in the Supporting Information.

Instruments

Stopped-flow experiments and absorbance spectra were collected on an Olis-RSM 1000 from Olis Inc, Bogard, GA, USA, with U.S.A. stopped-flow accessory using 120 µM slit widths and gratings of 400 lines/mm. The sample cell has a path length of 2 cm and a volume of 35 µL. All reactions were performed by flowing 0.25 mL of each reagent through the cell using a pneumatic piston pressurized by 80 psig compressed air. Temperature was controlled using a Julabo CF31 cryo-compact circulator from Julabo USA Inc., Allentown, PA, USA. Cyclic voltammetry experiments were conducted using a BASi Epsilon potentiostat and electrochemical cell from Bioanalytical Systems Inc. West Lafayette, IN, USA. Three electrodes were used: Pt working electrode, Pt wire auxiliary electrode, and a Ag/AgCl reference electrode, and KCl was used as the electrolyte.

General Procedure for Stopped-Flow Reaction of a Primary Intermediate with 3-Aminophenol (4) Using K₃Fe(CN)₆ as Oxidant

To a 5-mL volumetric flask was added a primary intermediate and phosphate buffer (I = 0.2 M) at the appropriate pH (9.25 or 10.3) until the final volume was 5 mL. The resulting mixture was sonicated in a 30°C bath until dissolved. An aliquot was added to a 10-mL volumetric flask, so that the final concentration of the primary intermediate was 100 µM. To a 5-mL volumetric flask was added 4 (19.6 mg, 180 µMol) and the appropriate pH phosphate buffer until the final volume was 5 mL. The resulting mixture was sonicated in a 30°C bath until dissolved. An aliquot (2.784 mL) was taken from the stock solution and mixed with the volumetric flask containing the primary intermediate aliquot. The solution was diluted to 10 mL with phosphate buffer (I = 0.2 M) at the appropriate pH bringing the concentration of 4 to 10 mM. The final solution was loaded into a 10-mL disposable syringe and placed at stopped-flow injection slot A. To a 5-mL volumetric flask was added K₃Fe(CN)₆ (45.9 mg, 139 µMol) and phosphate buffer (I = 0.2 M) at the appropriate pH to the to bring the volume to 5 mL. The resulting mixture was sonicated in a 30°C bath for 5 min. An aliquot (143 µL) was taken from the stock solution and diluted with the phosphate buffer (I = 0.2 M) at the

appropriate pH to 10 mL in a volumetric flask so that the final concentration was 400 µM. The solution was loaded into a syringe and replaced the buffer syringe located in injection slot B. The kinetic runs were carried out by injecting 0.25 mL of each syringe through the observation cell, bringing the reagents to the following final concentrations: [primary intermediate] = 50 μ M, [4] = 5 mM, and [K₃Fe(CN)₆] = 200 μ M. The rate was determined by observing the change in absorbance at the λ_{max} . The concentration of the dye formed was calculated using Beer's law, and the extinction coefficient of the dye was determined by the absorbance at t_{∞} . The first-order rate constant obtained under pseudo-first-order conditions was calculated by assuming a 1:1 mol conversion of primary to dye and plotting the ln[primary intermediate] versus time.

General Procedure for Stopped-Flow Reaction of a Primary Intermediate with 3-Amino-2,6-dimethylphenol Using K₃Fe(CN)₆ as Oxidant

To a 5-mL volumetric flask was added a primary intermediate and phosphate buffer (I = 0.2 M) at the appropriate pH until the final volume was 5 mL. The resulting mixture was sonicated in a 30°C bath until dissolved. An aliquot was added to a 10-mL volumetric flask and diluted with phosphate buffer (I = 0.2 M)at the appropriate pH, so that the final concentration of the primary intermediate was 100 µM. To a 5-mL volumetric flask was added 3-amino-2,6-dimethylphenol $(25.4 \text{ mg}, 184 \mu \text{Mol})$ and phosphate buffer (I = 0.2 M) at the appropriate pH until the final volume was 5 mL. The resulting mixture was sonicated in a 30°C bath until dissolved. An aliquot (2.700 mL) was taken from the stock solution and mixed with the volumetric flask containing the primary intermediate aliquot. The solution was diluted to 10 mL with phosphate buffer (I = 0.2 M) at the appropriate pH bringing the concentration of 3-amino-2,6-dimethylphenol to 10 mM. The final solution was loaded into a 10 mL disposable syringe and placed at stopped-flow injection slot A. To a 5-mL volumetric flask was added $K_3Fe(CN)_6$ (34.7 mg, 105 μ Mol) and phosphate buffer (I = 0.2 M) at the appropriate pH to bring the final volume to 5 mL. The resulting mixture was sonicated in a 30°C bath for 5 min. An aliquot (190 µL) was taken from the stock solution and diluted with phosphate buffer (I = 0.2 M) at the appropriate pH to 10 mL in a volumetric flask so that the final concentration was 400 µM. The solution was loaded into a syringe and replaced the buffer syringe located in injection slot B. The kinetic runs occurred by injecting 0.25 mL of each syringe

through the observation cell, bringing the reagents to the following final concentrations: [primary intermediate] = 50 μ M, [3-amino-2,6-dimethylphenol] = 5 mM, and $[K_3Fe(CN)_6] = 200 \mu M$. The rate was determined by observing the change in absorbance at the λ_{max} . The concentration of the dye formed was calculated using Beer's law, and the extinction coefficient of the dye was determined by the absorbance at t_{∞} . There are two phases for the reaction to form the dye species: (1) a rapid initial conversion directly to the dye and (2) a slower conversion from a nonproductive product formed by a side equilibrium. The first-order rate constant obtained under pseudo-first-order conditions for each step was calculated by assuming a 1:1 mol conversion of primary to dye and plotting the ln[primary] versus time.

General Procedure for Stopped-Flow Oxidation of a Primary Intermediate by K₃Fe(CN)₆

To a 5-mL volumetric flask was added a primary intermediate and phosphate buffer (I = 0.2 M) at the appropriate pH (7.9, 9.45, or 10.3) until the final volume was 5 mL. The resulting mixture was sonicated in a 30°C bath until dissolved. An aliquot was taken from the stock solution and diluted with phosphate buffer (I = 0.2 M) at the appropriate pH to 10 mL in a volumetric flask so that the final concentration was 100 µM. The final solution was loaded into a 10-mL disposable syringe and placed at stopped-flow injection slot A. To a 5-mL volumetric flask was added K₃Fe(CN)₆ (32.6 mg, 99.0 μ Mol) and phosphate buffer (I = 0.2 M) at the appropriate pH to bring the final volume to 5 mL. The resulting mixture was sonicated in a 30°C bath for 5 min. An aliquot (101 μ L) was taken from the stock solution and diluted with phosphate buffer (I = 0.2 M)at the appropriate pH to 10 mL in a volumetric flask so that the final concentration was 200 µM. The solution was loaded into a syringe and placed at stopped-flow injection slot B. The Julabo water circulator was set to 25°C. The solutions were allowed to sit in the loading syringes for 5 min for temperature equilibration. The kinetic runs were carried out by injecting 0.25 mL of each syringe through the observation cell, bringing the reagents to the following final concentrations: [primary intermediate] = 50 μ M and [K₃Fe(CN)₆] = 100 μ M. The rate was determined by observing the change in absorbance at 420 nm. K₃Fe(CN)₆ concentration was calculated by using $\varepsilon = 1000 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ at 420 nm and using the Beer's law. The initial rate was calculated by taking the slope of the line of $[K_3Fe(CN)_6]$ versus time over the first 10% of conversion.

Cyclic Voltammetry of a Primary Intermediate

A 0.1 M solution of KCl in water was used as the electrolyte. It was purged with N₂ for 15 min prior to collecting a background scan without the primary intermediate. Once the background scan had been collected, the primary intermediate (40 μ Mol) was added to electrolyte solution (5 mL) and pH adjusted to 10.0 \pm 0.02 using 0.1 M KOH. The solution was brought to 10 mL using the electrolyte solution and purged with N₂ for 2 min. Cyclic voltammograms were acquired from 0.6 to 1.2 V at 100 mv/s scan rate. After each run, the solution was allowed to stir for 1 min to ensure no solids were deposited on the probe.

RESULTS AND DISCUSSION

It has been observed that at alkaline pH color formation from $\mathbf{8}$ and some couplers is qualitatively different (and perhaps slower) than from $\mathbf{7}$. To help understand what might be driving this, we looked at two of the potential causes: rate differences for oxidation of $\mathbf{8}$ and reaction of its diimine with blocked and unblocked couplers.

Final indo dye formation from a primary intermediate and a blocked coupler such as **4** involves a two-step oxidation of the primary intermediate, electrophilic attack of the diimine on the coupler to form the leuco dye, and oxidation of the leuco dye to form the indo dye (Scheme 1). When potassium ferricyanide is used to mediate the oxidations, these steps drop from the rate expression because they are extremely rapid relative to the coupling step [1]. This allows straightforward derivation of a rate expression and determination of the rate constant for the coupling step. For our initial investigation of the coupling kinetics of **8**, we followed this convention.

The effect on final dye color and the rates of the oxidation and coupling steps caused by addition of

electron-donating groups to the primary intermediate, e.g., as a result of bis(2-hydroxyethylation) of the N(4) nitrogen, is well known [2,5]. In general, relative to the parent compound (1), electron-donating groups in the primary intermediate increase the rate of oxidation but decrease the rate of electrophilic coupling. Electronwithdrawing groups in the primary intermediate decrease the rate of oxidation, but increase the rate of coupling. Substituent effects are the reverse for couplers: Electron-withdrawing groups decrease the rate of coupling, and electron-donating groups increase the rate of coupling [2,5]. The kinetics of color formation from 2-substituted-benzene-1,4-diamines is not as well-studied as benzene-1,4-diamine, perhaps due to the potential complications that result from formation of product mixtures arising from coupling through the nonequivalent N(1) and N(4) nitrogens. This is true of 8; the methoxymethyl group has not been used in oxidation hair dye chemistry until recently, and its effects on rates of oxidation of the primary intermediate and the subsequent reaction of its oxidation product (the benzoquinonediiminium ion) with a coupler have not been explored. This is important as we understand the effect of the methoxymethyl substituent on the overall process.

Compound **8** also has the potential to exist in an H-bonded form (**8a**), as can its diimine (**9**) (Fig. 1). Owing to its electronegativity and its ability to form an H-bond with an adjacent amino or imino hydrogen, the oxygen atom of the methoxymethyl side chain of **8** has the potential to affect the electron density at the nitrogens attached to carbons 1 (N(1)) and 4 (N(4)) of 2-(methoxymethyl)benzene-1,4-diamine (**8**), its oxidized forms, and any of the intermediates or transition states in the dye-forming reaction (Fig. 1). Determining the impact on rate of coupling will help us understand this effect. Additionally, in either the non-H-bonded or H-bonded forms, there is the potential for steric interaction of the methoxymethyl side chain with the coupler to affect the rates.



Figure 1 Compound 8 and its diimine (9) showing the H-bonded and non-H-bonded forms.



Figure 2 Series of benzene-1,4-diamines and 3-aminophenols used as probes to elucidate contributions of steric and electronic effects on oxidation and coupling reactions in indo dye formation. For ring-substituted benzene-1,4-diamines, nitrogen N(1) is ortho to the carbon bearing the alkyl substituent, and N(4) is para to N(1).

Given that the electronic or steric differences from 1 and 7 could affect the overall rate, our goal was to understand at which step (if any) the effect was manifested, and the specific cause for that effect.

Effect of the Methoxymethyl Side Chain on Rates of Coupling

We used a series of benzene-1,4-diamines that potentially could help elucidate the roles of steric, electronic, and H-bonding effects on the rate of coupling (Fig. 2).

Relative to 1, 7 has the added electron-donating ability of the methyl group, without a large potential steric interaction. 2-Propylbenzene-1,4-diamine (10) is sterically similar to 8, but without the electronegative oxygen with its ability to H-bond. For this comparison among these primary intermediates, we used a sterically unhindered coupler, 3-aminophenol (11) and a sterically hindered coupler, 3-amino-2,6dimethylphenol (12).

The oxidation of benzene-1,4-diamine to its diimine, as ferricyanide is converted to ferrocyanide, is an equilibrium process. Corbett has demonstrated that reaction must be above approximately pH 8–8.5 for quantitative generation of the *p*-benzoquinonediimine which is necessary to isolate and understand the coupling step [7]. The final two steps in indo dye formation (formation and oxidation of the leuco dye) also can be viewed in aggregate as the rate of color formation, because conversion of the leuco dye to the indo dye (the final step of Scheme 2) is significantly faster than the attack of the p-benzoquinonediimine on the coupler under these conditions.

In the case of 11, Fig. 3 shows that the relative order of the coupling rates is $1 > 8 > 7 \simeq 10$. Recalling the general rule that any substituent that decreases the electron density at the nitrogen that attacks the electrophilic coupler, two things are apparent: (1) The methoxymethyl group is acting to withdraw electrons by H-bonding or inductive effects and is increasing the electrophilicity of the diimine of 8 relative to the other 2-substituted-benzene-1,4-diamine analogs (7 and 10), and (2) 1 seems to be out of order based on electron density at the reactive nitrogen. Additionally, the nearly identical rates of coupling for 7 and 10 support the importance of the role of electron donation to the ring by two alkyl substituents with similar Hammett σ values (Me, $\sigma_{\rm m} = -0.07$; $\sigma_{\rm p} = -0.17$; Pr, $\sigma_{\rm m} = -0.06$; $\sigma_{\rm p} = -0.13$) [13].

The Hammett σ values do not explain why coupling of **11** with **1** is faster than for **8** (CH₂OCH₃, $\sigma_{\rm m} = -0.10$; $\sigma_{\rm p} = 0.03$) [14]. If the reaction rate were controlled purely by the electronics, the series should be **8** > **1** > **7** \simeq **10**. For coupling of any of these primary intermediates through the unhindered N(4) with **11**, we would not expect any steric interactions that would decrease the rate. So with the exception of **1**, we could ascribe the differences to



Scheme 2 General reaction between 2-substituted-benzene-1,4-diamines and 3-aminophenols in which one or both of the 2and 6-positions may be substituted (blocked). Positional isomers for the cases in which R^1 is not –H are shown. Nitrogen N(1) is ortho to the carbon to which R^1 is bonded, and N(4) is para to N(1).

electronic factors. However, what must be considered in analysis of the rate data is that for 2-substitutedbenzene-1,4-diamines, coupling at both nitrogens is possible (Scheme 2), and N(1) (the nitrogen on the carbon ortho to the alkyl substituent) is more sterically hindered. In fact, it has been shown that although reaction at N(4) (the nitrogen on the carbon meta to the alkyl substituent) predominates, there is a significant amount of N(1) coupling product (Scheme 2) [15,16]. Slower reaction of the N(1) nitrogen could explain why the overall rates for this series seems to be out of order based on electronics with respect to **1**, in which the two nitrogens are equivalent, and there is no possibility of a rate disparity between the nitrogens. To provide further insight into whether steric interactions between the 2-substituent of the benzene-1,4diamine derivative affected coupling rate, we used **12** as the coupler. If electronic effects dominate, electron donation by the two methyl groups and a concomitant increase in nucleophilicity at the reaction site should result in a rate increase relative to **11**. If steric interactions significantly slow the rate of coupling with the N(1) nitrogen, the situation should be exacerbated by use of **12**. In that case, in some collisions between the a coupler–diimine pair either the amino or methyl group could interact with the 2-substituent of the diimine, and the collisions would not result in product formation.

As can be seen in Fig. 4 for reaction of **12** and **8**, conformation (b) is unfavorable and would limit



Figure 3 Observed rate constants under pseudo–first-order conditions as a function of pH for coupling of subject benzene-1,4-diamines with 3-aminophenol with $K_3Fe(CN)_6$ as oxidant in phosphate buffer (I = 0.2 M). [Color figure can be viewed at wileyonlinelibrary.com]



Figure 4 Two of the possible scenarios of coupler approaching benzoquinonediimine least hindered (a) and most hindered (b) configurations for coupling of **8** to **12**. The atoms and lone pairs are represented as gray for carbon, blue for nitrogen, red for oxygen, white for hydrogen, and pink for an electron lone pair. [Color figure can be viewed at wileyonlinelibrary.com]

electrophilic attack on 12 by 8. Of course, rotation on the C(3)–C(6) axis alleviates this poor orientation, but the possibility of unfavorable intermolecular interaction, or the requirement for specific geometric interaction of 12 and 8, has the potential effect of decreasing overall rate because not every intermolecular interaction (collision) can lead productively to dye formation.

We would expect similar steric interactions for **8** and **10**, perhaps less for **7** and none for **1**. This could cause an even greater disparity in coupling rates between **1** and the other primary intermediates.

In fact, the kinetics were not straightforward; we observed a biphasic kinetic plot, with a faster initial phase and a slower, eventually complete color formation, indicating that the process for **12** was different than for **11**. For reactions with **12** the overall rate of color formation (k_{obs}) is approximately 10^3 times slower than for **11** (Fig. 5).

Although the overall rate of coupling of the benzene-1,4-diamines with **12** was significantly slower than with **11**, we observed that initial rates of color formation are up to approximately 10 times faster than for the analogous reactions with **11**, as might be expected for a nucleophile that is more electron rich than the parent compound (Fig. 6). The initial rates of color formation were measured under pseudo–first-order conditions over the first few seconds of the reaction and were analyzed using the integrated rate law.



Figure 5 Observed rate constants for color formation under pseudo–first-order conditions at 25°C in phosphate buffer (I = 0.2 M) for 12 with subject benzene-1,4-diamines as a function of pH with $K_3Fe(CN)_6$ as oxidant. [Color figure can be viewed at wileyonlinelibrary.com]



Figure 6 Rates of coupling (color formation) at 25° C in phosphate buffer (I = 0.2 M) between 12 and dimine 13 (Scheme 3) for the fast initial reaction. [Color figure can be viewed at wileyonlinelibrary.com]

At both pH 9.25 and 10.3, contrary to the case with **11**, with **12**, the primary intermediates that are more electron rich than **8** have a higher rate of initial color formation. This is the reverse of what would be expected if there were no competing reactions. As mentioned earlier, electron-donating groups on the diimine should slow the reaction and electron-

withdrawing groups should increase the rate of coupling. Regardless, at pH 9.25 there is an indication that although the Hammett σ values for methyl ($\sigma_{\rm m} = -0.07$; $\sigma_{\rm p} = -0.17$) and propyl ($\sigma_{\rm m} = -0.06$; $\sigma_{\rm p} = -0.13$) are similar, there may be an effect exerted by increased steric interaction of the propyl group on rate.



Figure 7 Percent of total dye formation during the fast initial productive coupling step at 25°C between 12 and 13 at pH 9.25 and 10.3 in phosphate buffer (I = 0.2 M). [Color figure can be viewed at wileyonlinelibrary.com]

Given the biphasic nature of the reaction plots, the above indicates that an equilibrium process that has a slow reverse step is competing with the color-forming reaction, and that the diimines of **1** and **8** may react in a nonproductive manner more so than those of **7** and **10**. Analysis showed approximately 15–50% initial conversion to the indo dye, depending on pH and which primary intermediate was used, followed by a slower second phase in which complete conversion occurred (Fig. 7).

Corbett has noted a similar situation for 1 and 4 in which there was a nonproductive coupling (i.e., a dye is not formed) of 1 via electrophilic attack at the carbon ipso to the methyl group [1]. Apparently the methyl group is not completely efficient as a blocking group, but not unexpectedly, neither is it a good nucleofuge, such as a methoxy group [1,17–19]. So, although attack can occur to generate structure 14, the coupling is nonproductive and reversible. In Scheme 3, we show the process that begins with coupling of 12 and the *p*-benzoquinonediimine derivatives.

This nonproductive, reversible coupling of **12** with this series of benzene-1,4-diamines made the overall rates of dye formation much more similar across the series, and slower overall, than for coupling with **11** (Fig. 5).

It appears that the nonproductive pathway plays an important role in controlling the overall kinetics. Corbett has observed this for the case of benzene-1,4diamine and 5-amino-2-methylphenol [1], and we see the same behavior for 12. Above pH 8, the equilibrium between 1 and 13 lies far to the right, and the conversion to the diimine is "virtually instantaneous" [7,20]. Corbett also has reported [20] when a 1:4:1 ratio of a benzene-1,4-diamine:ferricyanide:coupler is used, both the benzene-1,4-diamine and the leuco dye are oxidized by ferricyanide, and the oxidation of the leuco dye occurs after the rate-limiting step [20]. In our case, i.e. Scheme 3, this means that coupling of 13 and 12 is the rate-determining step. Therefore, since we used a 4:1 molar ratio of ferricyanide:benzene-1,4diamine above pH 8, the conversions of the benzene-1,4-diamine derivative to leuco dye 13, and conversion of 15 to 16 are rapid; the kinetic expression is simplified (vide infra). Assuming that the oxidations of the are fast, the equations for Scheme 3 simplify as they did in Corbett's investigation, and we derive below the kinetic expression for oxidative coupling of 12 and 13:

$$\frac{\mathrm{d}\left[\mathbf{16}\right]}{\mathrm{d}t} = k_3 \left[\mathbf{15}\right] \left[\mathrm{Fe}^{\mathrm{III}}\right] \tag{1}$$

Assuming that **15** is at steady state, solving for **[15**] gives

$$\frac{d[\mathbf{15}]}{dt} = k_1[\mathbf{12}][\mathbf{13}] - k_3[\mathbf{15}] \left[\text{Fe}^{\text{III}} \right] - k_{-1}[\mathbf{15}] \simeq 0$$
(2)



Scheme 3 Reaction scheme depicting nonproductive equilibrium and productive color formation from diimine 13 and 12. For 13 nitrogen N(1) is ortho to the carbon to which R is bonded, and N(4) is para to N(1).

$$[15] = \frac{k_1[12][13]}{k_{-1} + k_3 \left[\text{Fe}^{\text{III}} \right]}$$
(3)

Substituting for [15] gives

$$\frac{\mathrm{d}[\mathbf{16}]}{\mathrm{d}t} = \frac{k_1 k_3 [\mathbf{12}] [\mathbf{13}] \left[\mathrm{Fe}^{\mathrm{III}}\right]}{k_{-1} + k_3 \left[\mathrm{Fe}^{\mathrm{III}}\right]} \tag{4}$$

If $k_3[\text{Fe}^{\text{III}}] \gg k_{-1}$, then

$$\frac{d[16]}{dt} = k_1[12][13]$$
(5)

For the nonproductive, reversible pathway

$$\frac{d[14]}{dt} = k_2[12][13] - k_{-2}[14]$$
(6)

once equilibrium has been established, it can be assumed that **13** is in a steady state giving

$$\frac{d[\mathbf{13}]}{dt} = k_{-1}[\mathbf{15}] + k_{-2}[\mathbf{14}] - k_1[\mathbf{12}][\mathbf{13}] - k_2[\mathbf{12}][\mathbf{13}] \simeq 0$$
(7)

$$[\mathbf{13}] = \left(\frac{k_{-1}[\mathbf{15}] + k_{-2}[\mathbf{14}]}{k_1[\mathbf{12}] + k_2[\mathbf{12}]}\right) \tag{8}$$

Substituting for [13] gives

$$\frac{d[\mathbf{16}]}{dt} = k_1[\mathbf{12}] \left(\frac{k_{-1}[\mathbf{15}] + k_{-2}[\mathbf{14}]}{[\mathbf{12}](k_1 + k_2)} \right)$$
(9)

$$\frac{d[\mathbf{16}]}{dt} = k_1 \left(\frac{k_{-1}[\mathbf{15}] + k_{-2}[\mathbf{14}]}{k_1 + k_2} \right)$$
(10)

Recalling that k_3 [Fe^{III}] $\gg k_{-1}$, and substituting for [15] in Eq. (9) gives

$$\frac{d[\mathbf{16}]}{dt} = k_1 \left(\frac{k_{-1}k_1[\mathbf{12}][\mathbf{13}]/k_3 \left[Fe^{III} \right] + k_{-2}[\mathbf{14}]}{k_1 + k_2} \right)$$
(11)

If $k_3[\text{Fe}^{\text{III}}] \gg k_1 k_{-1}[12][13]$, then

$$\frac{d[\mathbf{16}]}{dt} = \frac{k_1 k_{-2} [\mathbf{14}]}{k_1 + k_2} \tag{12}$$

For simplicity, we will define $k_1k_{-2}/(k_1+k_2)$ as k_{obs} , the overall rate of color formation, so we can represent

International Journal of Chemical Kinetics DOI 10.1002/kin.21110



Scheme 4 Oxidation of 2-substituted-benzene-1,4-diamines proceeds through two, one-electron steps, with aromaticity lost in the second step. Nitrogen N(1) is ortho to the carbon to which R is bonded, and N(4) is para to N(1).

the equation as

$$\frac{\mathrm{d}[\mathbf{16}]}{\mathrm{d}t} = k_{\mathrm{obs}}[\mathbf{14}] \tag{13}$$

The trend toward equalization of overall rates at a given pH is not adequately explained by just nonproductive equilibria, without considering the electronic properties that drive different rates for k_2 and k_{-2} among the primary intermediates. Because the active species in this type of coupling chemistry are the cationic diiminium ion and the phenolate [1], as pH is increased there are competing effects in the observed rates: an increase due to the increasing concentration of phenolate and a decrease due to the decreasing concentration of the diiminium ion. Because the pK_a should vary by substitution in each of these diiminium ions, the effect on the rate will be different for each benzene-1,4-diamine in our series, and we do not expect a clean trend in color formation rates across the series with 12 as pH is varied. Although we can make comparisons between individual pairs of molecules at a given pH value, we cannot make broad generalizations across the series without invoking the further conditions mentioned above. Since the Hammett σ values are similar for 7 (Me, $\sigma_{\rm m} = -0.07$; $\sigma_{\rm p} = -0.17$) and 10 (Pr, $\sigma_{\rm m} = -0.06; \sigma_{\rm p} = -0.13)$, we would expect the rates to be similar based on electronic factors and degree of protonation only. This is not the case at pH 9.25, and the rate disparity between them gives some hint to the importance of steric interaction as a driver of rates.

It is obvious that unlike for 11, when 12 is the coupler the initial rate of productive coupling is slower with 8 than with 7 or 10. This is not explained by a difference in the percent conversion; all reactions eventually go to completion. However, the rate of nonproductive coupling (k_2 vs. k_1) is fastest for 8. Since all reactions eventually go to completion and form the expected indo dyes, it appears to be a difference in kinetic control being operative to a greater extent for 8. This lends credence to the hypothesis that electronic effects of the substituents on the primary intermediate are important, and that as the Highest Occupied Molecular Orbital-Lowest Unoccupied Molecular Orbital (HOMO-LUMO) interactions change, nonproductive coupling can increase in importance in the process.

Although this has been informative and helps guide future work to fully understand the role that increased steric interaction might play in controlling the kinetics of the process, more conclusive work on the proposed steric interactions is necessary. By comparison of the results with **7** and **10**, this work does show that the methoxymethyl group of **8** is acting to increase the electrophilicity of the diiminium nitrogens. However, it does not explain adequately the observed differences indicated by Mohr-Hautavoine et al. [12]. Understanding the rates of oxidation of this series of benzene-1,4-diamines can help us answer our original question, though.

Effect of the Methoxymethyl Side Chain on Rate of Oxidation

It is known for benzene-1,4-diamines that oxidation to the corresponding *p*-benzoquinonediimine happens as two single electron oxidations (Scheme 4) [7,8,17]. We used 1, 7, and 8 to understand whether the methoxymethyl group was acting to decrease electron density, affecting the rate of either of these oxidation steps.

In the first step, aromaticity is maintained, but when the second electron is removed, there is loss of aromaticity. It is known that the substituents on the primary intermediates affect rates of oxidation, but it is unclear in this case whether that effect is through removal of the first or second electron. We used cyclic voltammetry to first validate that for 1, 7, and 8 each showed two distinct electron transfer steps. Table I shows that the oxidation potential for removal of the first electron (later shown to be rate determining) follows the series 7 < 1 < 8.

Having validated that these benzene-1,4-diamine derivatives were oxidized in two one-electron steps, we determined rates of oxidation by potassium

Table I Average Values for Removal of First and Second Electrons [E / V vs. Ag/AgCl (3 M KCl), pH 10.0] for $1,\,7,\,{\rm and}\,8$

Compound	E_1 (V)	E_2 (V)
1	0.242	0.444
7	0.212	0.37
8	0.275	0.423

ferricyanide by monitoring the conversion of ferricyanide to ferrocyanide at 420 nm in a stopped-flow apparatus. Examining the initial rates and attempting to fit the data to both first- and second-order equations verified that the reaction was second order overall with first-order dependence on both the benzene-1,4diamine derivative and potassium ferricyanide. Figure 8 shows the second-order rate constants for complete oxidation at three pH values.

The series follows exactly the order that would be expected based on the Hammett σ values of the substituents: **7** (Me, $\sigma_m = -0.07$; $\sigma_p = -0.17$) with its electron-donating substituent, is faster than the benchmark (**1**) (H, $\sigma_m = 0.00$; $\sigma_p = 0.00$) and the methoxymethyl group (CH₂OCH₃, $\sigma_m = -0.10$; $\sigma_p = 0.03$) of **8** is acting to withdraw electrons from the ring and to decrease the rate of oxidation relative to **1**. In fact, the rate of the first oxidation of **7** is approximately double that of **8** across the pH range, explaining the previous observations of Mohr-Hautavoine et al. on color formation [12].

CONCLUSIONS

In simple reactions such as with **11**, clear guidance is available to understand how to exploit the color-forming reactions of this series of benzene-1,4-diamines, and in particular 2-(methoxymethyl)benzene-1,4-diamine. Although the overall observed rate was somewhat slower for **8** than for **1**, the rate of coupling of **8** with **11** actually is faster than for the other 2-substituted-benzene-1,4-diamines (**7** and **10**).

When more substituted primary intermediates (with multiple coupling sites) and couplers with additional substituents are employed, kinetics becomes more complex. For primary intermediates, it is possible to add substituents to the molecule to slow or accelerate the rate of oxidation to make it more controllable while also impacting the HOMO–LUMO interactions with the coupler. Knowledge of these effects makes it fairly easy to inform the design of new dye materials and to direct the chemistry. In addition to these electronic effects, steric interactions also play an important role in overall color formation rates, as is demonstrated for **1** versus substituted primary intermediates.

Removal of the first electron from the primary intermediates is rate determining, and the rate constants for that step follow the expected order, 8 < 1 < 7. As Feng and Chan showed, this is especially important in indo dye formation chemistry when milder (slower) oxidants are used, such as in haircolor products [21], and the oxidation of benzene-1,4-diamines by H₂O₂ is the rate-determining step in color formation.



Figure 8 Rate constants for oxidation of 1, 7, and 8 by $K_3Fe(CN)_6$ at 25°C in phosphate buffer (I = 0.2 M) at pH 7.9, 9.45, and 10.3. [Color figure can be viewed at wileyonlinelibrary.com]

14 BAILEY, ZHANG, AND MURPHY

We have not distinguished between the pure inductive effect of the methoxymethyl group and the contribution of H-bonding. It is clear from the work of Corbett and others that the transition state in the ratedetermining step should involve a charge, and therefore future work investigating kinetic isotope and salt effects should yield answers on this point. Additionally, we plan to investigate more thoroughly the role of H-bonding through NMR and crystallography.

Finally, we have not examined the mechanism of the reverse step of nonproductive coupling. Further work is needed to determine how the seemingly kinetically preferred product (14) is being converted to indo dye 16.

AUTHOR CONTRIBUTIONS

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

NOTES

The authors declare no competing financial interest.

The authors acknowledge Dr. Bob Strife for acquiring the HRMS data, Dr. Keith Brown for ongoing discussions and insights on oxidation dye chemistry, Dr. John Gardlik for his helpful comments on mechanistic details, and Dr. Bill Laidig for his molecular modeling and calculations.

BIBLIOGRAPHY

- 1. Corbett, J. F. J Chem Soc, Perkin Trans 2 1972, 539– 548.
- Morel, O. J. X.; Christie, R. M. Chem Rev 2011, 111, 2537–2561.
- 3. Wella AG, US Patent 6, 2003 558, 433 B2, 2003.

- Goebel, C.; Troutman, J.; Hennen, J.; Rothe, H.; Schlatter, H.; Gerberick, G. F.; Blömeke, B. Toxicol Appl Pharmacol 2014, 274, 480–487.
- Murphy, B. P. Hair Colorants, In: Poucher's Perfumes, Cosmetics and Soaps, 10th Ed., Butler, H. Ed.; Kluwer Academic Publishers: London; 2000: Chapter 10.
- Bailey, A. D.; Murphy, B. P.; Guan, H. J Phys Chem A 2016, 120, 8512–8520.
- 7. Corbett, J. F. J Chem Soc (B) 1969, 207-212.
- Tong, L. K. J. J Phys Chem 1954, 58, 1090– 1097.
- Henkel AG & Co. KGaA. German Patent Application DE 10 2008 061 864 A1, 2010.
- 10. Henkel AG & Co. KGaA. European Patent EP 1 765 267 B1, 2010.
- 11. L'Oreal. World Patent Application WO 2010133639 A1, 2010.
- 12. Mohr-Hautavoine, C. V.; Herrlein, M.; Guthrie, J. T. Dyes Pigments 2015, 117, 157–162.
- 13. Hansch, C.; Leo, A.; Taft, R. W. Chem Rev 1991, 91, 165–195.
- Perrin, D. D.; Dempsey, B.; Serjeant, E. P. pK_aPrediction for Organic Acids and Bases; Springer Publishing Company: New York, NY, 1981.
- Scientific Committee on Consumer Products, Opinion on Intermediates and reaction products of oxidative hair dye ingredients formed during hair dyeing, SCCP/1198/08, Adopted at the 19th plenary meeting of 21 January 2009.
- Scientific Committee on Consumer Products, Opinion on Reaction Products of Oxidative Hair Dye Ingredients Formed during Hair Dyeing Processes, SCCS/1311/10, Adopted at the 8th plenary meeting of 21 September 2010.
- 17. Corbett, J. F.; Brown, K. C. J Chem Soc, Perkin Trans 2 1972, 1125–1131.
- Corbett, J. F. J Chem Soc, Perkin Trans 2 1972, 999– 1005.
- Brown, E. R. In: The Chemistry of Quinoid Compounds, Vol. II; Patai, S.; Rappoport, Z. Eds.; Wiley : Hoboken, NJ, 1988; pp. 1231–1292.
- 20. Corbett, J. F. J Soc Cosmet Chem 1973, 24, 103–134
- 21. Feng, Y.; Chan, A. J Soc Cosmet Chem 1994, 45, 299– 308.