CHEMICAL REVIEWS

REVIEW

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Current Trends in the Chemistry of Permanent Hair Dyeing

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1. INTRODUCTION

Hair is one of the most distinctive elements of our appearance. The natural color of hair commonly reflects an individual's geographic or ethnic origin.[1] Hair is commonly colored with synthetic dyes to enhance its appearance or as a fashion statement. History has highlighted hair coloration as one of the oldest acts of adornment,[2] reflecting a perennial dissatisfaction with natural hair color. As a consequence, hair dye manufacture has developed over the years into a multinational multibillion dollar industry.[3] Most of its income (ca. 70%) is derived from permanent hair dye products, which owe their popularity to their long-lasting effect, ease of application, and versatility, allowing virtually any color to be achieved. As a result of an increasingly aging, and thus greying, global population, demand for these products has been increasing rapidly, a trend likely to continue into the future.[4] The processes used in hair coloration have unique features that distinguish them from, for example, textile dyeing. As a process carried out on the human head, hair cannot be dyed above ~40 °C, with a dyeing time generally not exceeding ca. 40 min, and a small liquor-to-fiber ratio (1−2:1), which in this case refers to the ratio of the volume of the wet hair dyeing formulation to the weight of hair to which it is applied. Coloration must not impair the natural texture or gloss of the hair or stain the scalp.[5] The color must be stable to air, light, friction, perspiration, and chlorinated water, and remain unaffected by other hair treatments. Critically, the dyeing process must be toxicologically safe. Human hair grows by ~0.3 mm each day on average, the growth cycle lasting about 7 years until the hair falls out. The use of the term *permanent* to designate the longest-lasting hair coloration effect is thus qualified by this feature, because further treatment is needed every 4−6 weeks to cover new growth.

The chemistry of permanent hair dyeing technology is based on a 150-year-old observation by Hofmann[6] that *p*-phenylenediamine produces brown shades on a variety of substrates when exposed to oxidizing agents, including air. Perhaps surprisingly in view of subsequent immense advances in chemistry, this still forms the basis of the most commonly used hair coloration process. Concerns about the human safety profile of some hair dye precursors have been raised throughout the years.[7] Because of their widespread use in which direct human contact is involved, the chemical structures of some ingredients, which are aromatic amines, and a few signals in the epidemiological literature, the human safety profile of hair dye ingredients has been studied extensively, and some original ingredients are now prohibited.[8] Contact allergy arising from some hair dye components can arise, and manufacturers have introduced risk management measures to reduce allergenic potential.[9] Two relatively recent publications describe the results of extensive international epidemiological studies on the link between hair coloration and more serious human conditions.[10,11] The authors of these articles, who draw attention to inconsistencies in other studies, indicate that the personal use of hair coloration may play a role in the risk of certain lymphomas. The increased risk is described as moderate and much more significant among women who had used the dyes before 1980 when the compositions would have been more likely to include potentially carcinogenic components. In parallel, the industry continues to provide reassurances over the formulation ingredients in current use.[12] For example, the European Commission has requested that the safety profile of all hair dye ingredients currently in use in the EU should be updated according to most recent standards and reviewed by appropriate EU scientific committees, in an ongoing process designed to provide reassurance on the human safety of oxidative hair dye ingredients. Nevertheless, a change to the situation cannot be excluded in the future as stricter legislation, regulations, and controls on the use of chemicals emerge. In Europe, the safety of hair dyes is controlled by a Cosmetic Directive

Received: January 14, 2010
Published: January 25, 2011

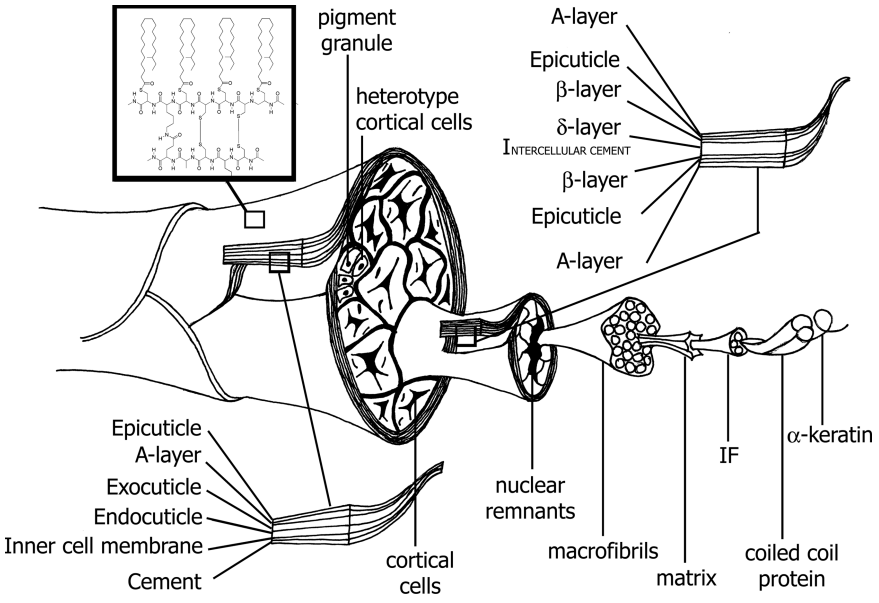


Figure 1. Structure of human hair.[25]

including two annexes dating from 1976 but still currently valid.[13] A scientific committee of the European Commission (SCCNFP, Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers) advises the EU on the safety of hair dyes. In the United States, the legal responsibility rests with the FDA.[14] In 1976, the CTFA (Cosmetics, Toiletry and Fragrance Association) established a CIR (Cosmetic Ingredient Review), an independent expert panel for the safety of cosmetic ingredients. The CIR published safety assessments of cosmetic ingredients that were qualified as *safe as used* or *safe under specific use restrictions*. In Japan, the Ministry of Health, Labour and Welfare (MHLW) regulates the safety of hair dyes, considering them as "quasi-drugs", subject to approval based on evidence of their safety. Other Far Eastern countries, including Korea, Taiwan, and China, have their own regulatory schemes for hair dyes that are similar to those practiced in Japan. Discussion of the detail of the legislation dealing with hair dye use is beyond the scope of the present review with its focus on the chemistry, because of its complexity, its variability from country to country, and its dynamically changing nature. For example, this review has been produced during the process of implementation of REACH in Europe, and it remains to be seen how its full implementation will impact on legislation and regulation of hair dyes.

Manufacturers have in recent decades embarked on intense research toward new dyes and precursors, as well as into alternative technologies for permanent hair dyeing. This research has been aimed not only at addressing potential toxicological issues but also technical weaknesses such as inadequate lightfastness. There are several previous reviews on aspects of hair dyeing,[15−20] although most are either considerably dated or very general in nature. In view of the current situation, this review is timely in that it encompasses our current understanding of the established permanent hair dyeing process, together with developments toward new technological approaches. Its comprehensive coverage is based on literature and patents (mainly U.S.) from 1975 to 2009, although reference to key early patents is also made. The review also provides an overview of the physical and chemical structural features of the hair fiber that are of importance in hair dyeing and of the species which give rise to natural hair color.

2. STRUCTURE AND MORPHOLOGY OF HUMAN HAIR[21−23]

Human hair grows from elongated sacs, the follicles or roots. These follicles are generated from cells that multiply under the skin creating a budlike structure. Cells in the deeper part of the follicle move upward to the epidermis, and the hair shaft pierces the superficial layer of the skin. These embryonic processes continue throughout the hair growth cycle.[24] Human hair differs in macroscopic structure, with three different types identified. Caucasian hair is generally fine and straight to curly. Its cross section is nearly circular (ellipticity 1.25). Ethiopian hair is coarse and wavy to woolly with a slightly oval cross section (ellipticity 1.75). Mongolian hair is coarse and straight to wavy with a similar cross section to Caucasian hair (ellipticity 1.35).

A fully formed hair fiber contains four units: the cuticle, cortex, medulla, and cell membrane complex (CMC). The cuticle contains an outer layer of flat overlapping scales, forming 6−10 cell layers that completely surround the hair.[26,27] This coating protects the hair against external damage.[28−30] The edges of the scales run circumferentially around the fiber, attached at the proximal (root) end and pointing toward the distal (tip) end. The cuticle is not highly organized at the molecular level. Its internal structure is illustrated in Figure 1. Each cuticle cell contains a thin (5−10 nm) outer membrane, the epicuticle (F-layer). Models of this layer have been proposed in which a fatty acid layer is connected to the underlying fibrous protein layer through thioester linkages to cysteine protein residues as illustrated in Figure 1.[31−35] This feature explains the apparent hydrophobic character of the hair fiber and is of importance in hair dyeing mechanisms. Beneath the outer membrane layer, the cuticle contains three other major layers: the A-layer (ca. 120 nm) with a high cystine content and highly cross-linked; the exocuticle (B-layer), also rich in cystine, occupying about half the cell volume; and the endocuticle, a layer of low cystine content and relatively high levels of dibasic (lysine, arginine) and diacidic (aspartic, glutamic) amino acids. Surrounded by the cuticle layer is the cortex, which contains most of the fiber mass. Cortical cells are generally 1−6 μm wide

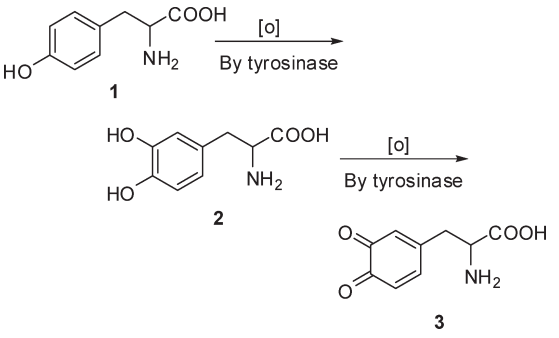
dx.doi.org/10.1021/cr1000145 |*Chem. Rev.* 2011, 111, 2537–2561

and ca. 100 μm long, although size, shape, and chemical composition may vary with location. Cortical cells adjacent to the cuticle (referred to as heterotype) are flatter and contain less sulfur than cells in the bulk of the cortex. On average, compared to the cuticle, the cortex is richer in cystine, diacidic amino acids, lysine, and histidine. Cortical cells also contain pigment granules (small, oval, or spherical particles) and nuclear remnants (small, elongated cavities near the center). They have a pronounced substructure, with microscopically discernible spindle-shaped macrofibrils (ca. 0.1−0.4 μm in diameter) composed of intermediate filaments (IFs) or microfibrils, highly organized units embedded in a less structured matrix. The IFs (diameter ca. 7.5 nm), are arranged in a spiral formation in the cortical cells, although incompletely characterized.[36] They contain precise arrays of low-sulfur proteins, with short sections of helical proteins in a coiled formation.[37,38] The coiled sections of these proteins chains are ca. 1 nm in diameter, and approximate to an α-helical form, explaining why hair proteins are referred to as α-keratin. The matrix is the largest structural subunit of the cortex. Although often referred to as the amorphous region, it has some limited structural organization. It contains the highest concentration of disulfide bonds and contributes significantly to the swelling behavior of the hair. Thin human scalp hair (diameter < 60 μm) consists of cuticle and cortical cells only. Hairs of larger cross section have a third cell type, the medullary cells, located in the center of the fiber. Medullary cells are loosely packed and spongelike with pores, bridges, and cavities. Often, the medulla comprises only a small number of keratin fibrils and can serve as a pigment reservoir. It is believed to contribute to the shine of hair.[39] The CMC consists of cell membranes and adhesive material that binds the cells together. Its outer lipid layer forms the epicuticle. The inner layer, referred to as the intercellular cement (Figure 1), is located between the cuticle cells, consisting of a δ-layer, which includes proteins low in cystine (<2%) but high in polar (ca. 12% basic amino acids and 17% acidic) amino acids. The δ-layer is sandwiched between two inert lipid-containing β-layers.[40] The structure of lipid bilayers with the embedded membrane proteins undergoes changes as the hair fiber grows, although the structural array of adjacent cell membranes remains unchanged. Also, further cell connections at the interface between the cuticle and the heterotype cortical cells appear. The CMC and the endocuticle are commonly referred to as the nonkeratinous regions because of the comparatively low level of sulfur-containing amino acids. It is believed that these regions provide important pathways for diffusion of molecules into the hair fiber.

3. NATURAL COLOR OF HAIR

Nature provides an abundance of hair colors and shades ranging from light blond, prevalent among Scandinavians, to black, characteristic of Asians, Arabics, southern Europeans and Africans. Between these extremes, the hair of middle and northern Europeans shows a wide variety of browns, and red hair originates in Celtic countries. Natural hair colors exist in a small segment of CIELAB color space,[41] corresponding to dominant absorption wavelengths between 586 and 606 nm, while lightness (L^*) varies over a wide range from 1.8 to 90%. Natural hair color is due to the presence of the pigment melanin in the cortex and medulla, in the form of granules, ca. 1 μm long and 0.3 μm in diameter.[42] Melanin is formed in pigment-producing cells

Scheme 1. Oxidation of Tyrosine (1) to Dopaquinone (3) via DOPA (2)



(melanocytes) in the follicle during the growing phase. Initially, these granules (melanosomes) consist primarily of a protein (melanoprotein). As the granules mature, the protein binds increasing amounts of melanin, which is then transferred from the melanocytes into adjacent keranocytes. Thus, as hair grows, it acquires its color, lasting throughout the lifetime of the hair. A melanocyte produces essentially two types of melanin:[43] *eumelanin* and the less prevalent *pheomelanin*.[44] Eumelanin granules are ovoid or spherical, fairly uniform in shape, with sharply defined edges. Their color varies from reddish-brown to black. Pheomelanin granules are smaller, partly oval and partly rod-shaped, with color varying from blond to red. Generally, hair contains a mixture of the two pigments; the more eumelanin, the darker the hair. Japanese black hair contains virtually only eumelanin and this pigment also predominates in Mongolian, Ethiopian, and dark Caucasian hair. Celtic red hair is rich in pheomelanin, whereas Scandinavian blond hair contains mainly eumelanin at low levels. The wide color range arises from not only the concentrations of the two pigments but also the size and shape of the granules, the distribution patterns,[45] and the crystal structures.[46] However, the interrelationships remain incompletely understood.[47]

Although the two pigment types have distinct characteristics, the biosynthetic routes are closely related. They are formed from a series of enzymatic reactions, with amino acid tyrosine (**1**) as the common starting material. As illustrated in Scheme 1, hydroxylation of tyrosine facilitated by tyrosinase, an oxidase containing trace amounts of copper(I), forms 3,4-dihydroxyphenylalanine (DOPA, **2**). The enzyme induces further oxidation to form dopaquinone (**3**).

At this stage, a divergence separates the biosynthetic pathways leading to the two melanin types.[48,49] Scheme 2 illustrates the route which ultimately generates eumelanin. A cyclization converts **3** into leucodopachrome (**4**). Oxidation leads to the red dopachrome (**5**), which undergoes rearrangement to 5,6-dihydroxyindole-2-carboxylic acid (DHICA, **6**). Decarboxylation then leads to 5,6-dihydroxyindole (DHI, **7**) which is oxidized to indolequinone (**8**), a highly reactive intermediate from which an oxidative polymerization is initiated leading to eumelanin. Initial proposals that eumelanin was produced via oxidative homopolymerisation of DHI **7**[50−54] represent an oversimplification, because it is known to be a complex copolymer.[55,56] Nicolaus proposed a random polymeric structure formed from several species containing repeat units incorporating proteins, carbohydrates, and nucleic acids.[57] Swan[58] and Ito[59] have proposed oxidative mixed polymerization involving **7** and several

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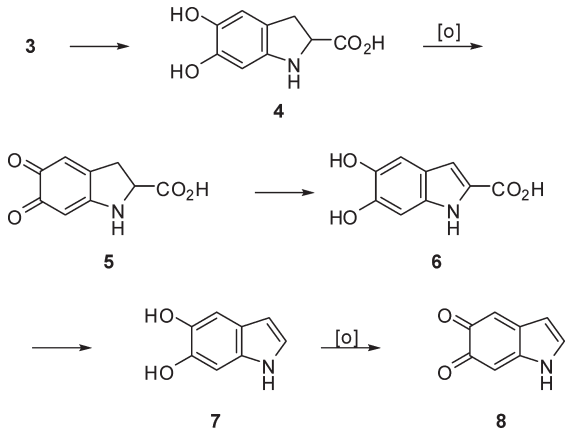
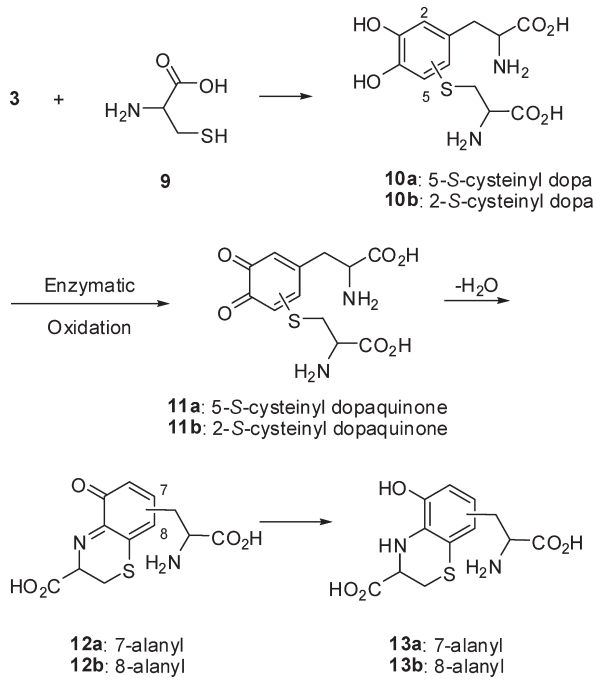
Scheme 2. Biosynthesis of Precursors to Eumelanin



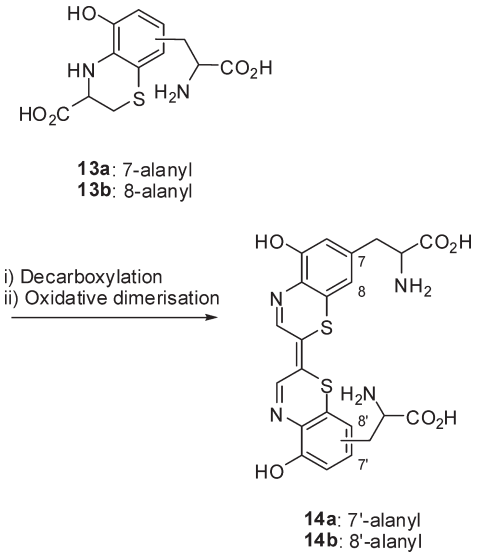
Scheme 3. Biosynthesis of Precursors to Pheomelanin Pigments



other of the intermediates shown in Schemes 2 and 3, leading to a nonhomogeneous, graphite-like polymer.[60] Details of the polymerization have yet to be elucidated, but oligomeric species leading to an unpredictable random structure are likely to be involved.

Elemental analysis shows that pheomelanin has a much higher sulfur content than eumelanin.[49] Pheomelanin pigments are polymers containing benzothiazole and tetrahydroisoquinoline units, with minor amounts of units based on $\Delta^{2,2'}$-bis(1,4-benzothiazine).[61−63] Pheomelanin pigments are also derived biosynthetically from dopaquinone (**3**).[64] As illustrated in Scheme 3, this precursor reacts with the amino acid cysteine (**9**) by 1,6-addition to give 5-*S*-cysteinyl DOPA (**10a**) and, to a lesser extent, 2-*S*-cysteinyl DOPA (**10b**).[65−67] Enzymatic oxidation of **10a** and **10b** gives quinones **11a** and **11b**, respectively,

Scheme 4. Biosynthesis of Trichochrome Pigments E and F



which cyclize with elimination of water to form quinoneimines **12a** and **12b**, respectively. Reduction leads to intermediates **13a** and **13b**. If the reducing agents are **10a** and **10b**, further quantities of **11a** and **11b** are generated to sustain the process. Details of the biosynthesis of pheomelanin beyond the dihydrobenzothiazine stage are uncertain. However, it is known that 2*H*-1,4-benzothiazines readily undergo oxidative dimerization. In this way, it is proposed that trichochrome pigments may well be formed during the biogenesis of pheomelanins. As illustrated in Scheme 4, decarboxylation of **13a** followed by oxidative self-dimerization would give the violet trichochrome F (**14a**). Decarboxylation of **13b** followed by oxidative dimerization with the product of decarboxylation of **13a** would give trichochrome E (**14b**).

Scheme 5 shows the sequence of reactions by which **12a** and **12b** are converted via intermediates **15**, **16**, and **17** to lactams **18a** and **18b**. Oxidative dimerization of **12b** with **18a** would produce trichochrome B (**19a**), and that of **12a** with **18a** would produce trichochrome C (**19b**). Trichochromes B and C have been identified in hair together with isomers **19c** and **19d**.[63]

The partial structures given in Figure 2 represent a current view approximating to the general structure of the pheomelanin pigment,[49] which is an irregular polymer. Since benzothiazoles have not been detected prior to pigment formation, it is believed that polymerization occurs at the benzothiazine stage, and a subsequent ring contraction hypothesis has been postulated.[68] To account for the visible absorption, it is likely that some of the phenolic rings in structure **20** are converted to a quinonoid form, as possibly in structure **21**.

The control mechanisms leading to divergence of the biosynthetic pathways toward either eumelanin or pheomelanin remain unknown. Cysteinyl DOPA and its metabolites are found in hair of both eumelanic and pheomelanic subjects.[69] Thus, each individual has the capability to produce either melanin type. Recent studies have revealed the formation of a copolymer of eumelanin and pheomelanin, suggesting an interaction between the two pathways.[70] It is interesting that, whereas nature uses only two species to produce its variety of colors, the hair dye chemist needs many colorants to produce the range of commercial synthetic hair colors.

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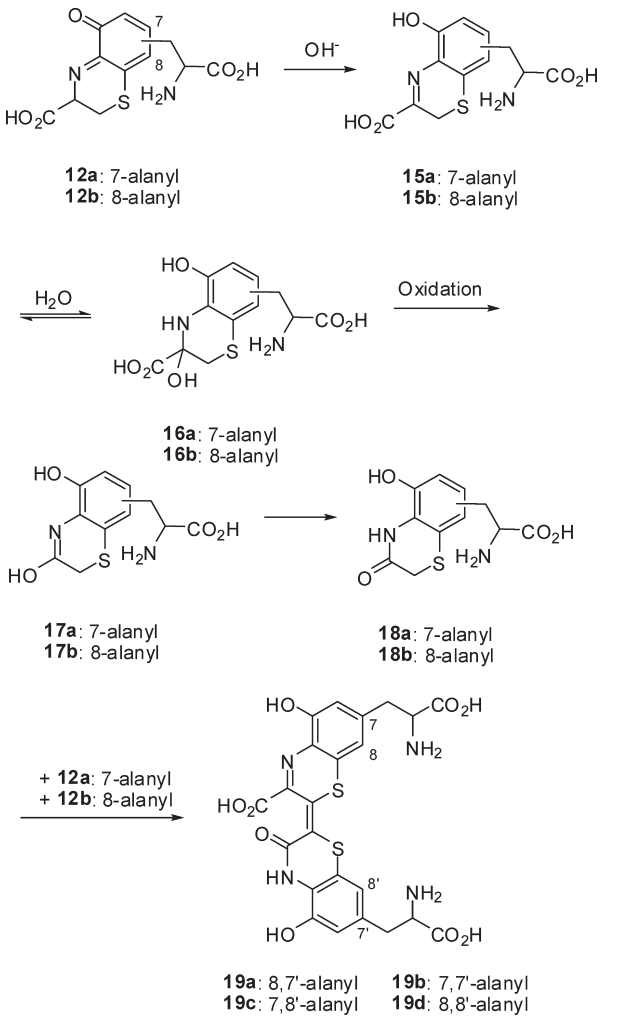
Scheme 5. Biosynthesis of Trichochromes pigments B and C



4. PHYSICAL CHEMISTRY OF HAIR DYEING

There have been several studies aimed at establishing the diffusion pathways followed by molecules as they penetrate into hair fiber, of evident significance to dyeing processes. Two theories, intercellular and restricted transcellular diffusion mechanisms, have been the subject of ongoing debate.[71−74] Intercellular diffusion involves permeation of molecules into the intercuticular regions, from where they diffuse into the nonkeratinous regions, the endocuticle and the intercellular cement. In later stages of dyeing, the molecules migrate into the sulfur-rich keratinous region, from the endocuticle to the exocuticle, eventually reaching the macrofibrils, where they are incorporated into the matrix.[75,76] This latter phenomenon is typical of the behavior of wool, also a protein fiber, during dyeing with sulphonated dyes, where it is observed that the nonkeratinous regions, although involved in the early stages of dyeing, are virtually devoid of dye at the end of the process when the dyeing temperature is increased to > 90 °C.[77] In the case of hair dyeing, this mechanism proposes that the intercellular cement offers a continuous pathway to the center of the fiber, aided by its ability to swell and, thus, facilitating dye uptake.[78] The restricted transcellular diffusion mechanism considers that molecules penetrate the hair fiber through the endocuticle of the cuticle cell

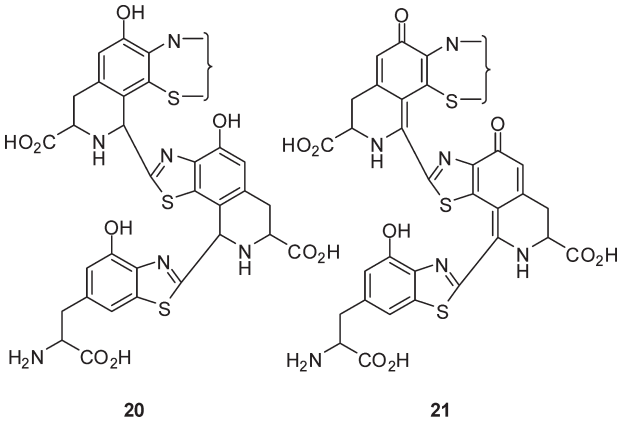


Figure 2. Proposed partial structures characteristic of pheomelanin.

edge rather than via the CMC.[79] Molecular diffusion into the hair fiber from one cell to the next takes place through occasional adventitious holes in the CMC.[80] A feature that contrasts these two theories is the role of the intercellular cement (the δ-layer), which adopts an integral role in the former but is probably minor in the latter. The opinion has been expressed that a method to measure the swelling of the intercellular cement in situ will be required to provide a resolution to the debate.[74] The use of microdiffraction has demonstrated a 10% swelling of δ-layer thickness when the hair was immersed in a water-filled capillary,[81] providing evidence that the size of the δ-layer may not be not an obstacle to intercellular diffusion. It has been shown that water-soluble molecules may access all components of hair, although the diffusion pathway and their final location may differ with molecular structure.[82] Reinforced by other studies,[83] it was concluded that, for "small and active molecules", there is a transport system within which the CMC, with its ability to swell, provides the pathway by which molecules are conducted by capillary forces toward the cortex.

The pH of choice for hair dyeing is generally in the range 9−10. At alkaline pH, significant swelling is observed, most likely primarily due to ionization of diacidic amino acid residues. The isoionic point, the pH at which a protein has an equivalent number of positive and negative charges, and the isoelectric point, the pH at which a protein does not migrate in an electric field, are relevant to hair dyeing mechanisms. The isoionic point of hair has been determined on unaltered hair, giving values of pH 5.8 ± 1, whereas the isoelectric point of a single hair sample is reported as pH 3.67.[84] Thus, under alkaline conditions, hair will have stronger affinity for cationic than for anionic dyes by virtue of its negative charge. An investigation into drug penetration in hair in forensic analysis provides an interesting insight.[85] At its isoelectric point, where hair is essentially neutral, the major intermolecular interactions are weak hydrophobic forces due to the hydrophobicity of the hair fiber surface. As the pH increases, there is enhanced interaction of negatively charged hair with positively charged drug molecules, such as cocaine or morphine. Of special interest is the ionic character of the CMC and the endocuticle, the two components mainly involved in the diffusion of dyes into the fiber, in both of which acidic amino acids predominate over basic amino acids. Another relevant feature is the effect of oxidative bleaching of hair, which significantly increases the number of anionic groups through cysteic acid formation.

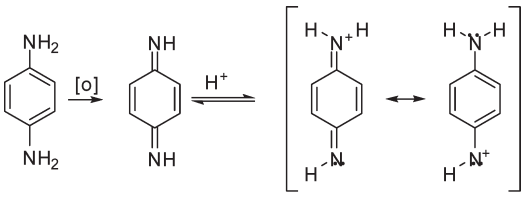
dx.doi.org/10.1021/cr1000145 |Chem. Rev. 2011, 111, 2537–2561

A critical factor that governs the penetration of a dye into the hair fiber is molecular size.[86] A model for keratin fibers proposed as a solid constructed from "micelles",[87] although subsequently shown to lack rigorous justification, provided early recognition of the influence of molecular size on dye diffusion. Many years later, the concept of a critical molecular size for penetration into hair fiber was reinforced, based on microscopic investigations of cross sections of human hair dyed with dyes and dye precursors.[88] Assuming spherical molecules, it was proposed that dyes with molecular diameters > 6 Å were prevented from penetration into hair. In a complementary independent study, hair was likened to a sieve and, also considering spherical molecules, a sieve hole size of 14.8 Å was estimated.[89] The different results of these two studies may be rationalized in that the investigators used quite different dyeing conditions and hair samples. In a more definitive study, Sakai et al.[90] introduced the concept of "the longest diagonal line of the smallest shadow of the projected figure" (S_{LD}) as a measurement of molecular size that also takes account of molecular shape to some extent. They correlated experimental permeation distances of selected fluorescent dyes into hair with calculations of S_{LD} through molecular modeling, concluding that molecules with S_{LD} values < 10 Å migrate much more easily into hair. We have subsequently published a reevaluation of these original experimental data correlated with results of calculations based on more sophisticated molecular modeling methodology (XED98), and have proposed a revised descriptor of size, L_D, the longest dimension of the smallest cross section of the optimum parallelepiped enclosing the molecule, as a measure of the diffusivity of the dye into the fiber. On the basis of this analysis, a size limit of ca. 9.5 Å was proposed for nonionic dyes with slightly larger size limits for ionic dyes.[91] In practical terms, the pore sizes and the consequent effect on dye diffusion will also be affected by fiber swelling, in turn influenced by factors such as the nature and concentration of other hair dye formulation ingredients, such as solvents.

5. PERMANENT HAIR COLORATION: AN OXIDATIVE PROCESS

The first hair coloring process based on Hofmann's observation was patented 20 years after his discovery.[92] Modern commercial hair coloring products can be divided conveniently into two main categories according to the chemistry involved: oxidative and nonoxidative process. The latter group, which includes semipermanent hair dyes, is beyond the scope of this review and has been covered elsewhere.[93] Oxidative dyeing products may be further divided into three subcategories: permanent hair dyes, demipermanent hair dyes, in which the hair is lightened less and the colors fade with time, and autooxidative hair dyes, which offer the users, particularly males, color development over a period of time.[1] Permanent hair coloration requires three main components. The first is an *o*- or *p*-substituted (hydroxy or amino) aromatic amine, referred to as the primary intermediate, oxidation base, or developer (by analogy with color photography). Primary intermediates include *p*-phenylenediamine, *p*-aminophenol, and their derivatives. The second component, the coupler, is commonly an aromatic compound with electron-donating groups arranged meta to each other, including *m*-phenylenediamines, resorcinol, naphthols, and their derivatives. These compounds alone do not produce significant colors by oxidation but modify the color when used with the primary intermediates and an oxidant. Couplers are classified into three groups, according to the color obtained in the fiber with the primary intermediates: yellow−green, red, and blue. The third component is the oxidant, almost exclusively hydrogen peroxide (although in special cases atmospheric oxygen can be used) with an alkali, usually ammonia. The oxidant serves two main purposes: to oxidize the primary intermediates and, in combination with ammonia, to lighten the natural hair color. A reduced level of bleaching is achieved using a "no-ammonia" alkalizer, typically monoethanolamine. The bleaching effect may be completely eliminated while still allowing effective color development using sodium carbonate or aminomethylpropanol. Permanent hair coloring preparations are generally marketed as a two-component kit. The first component contains the dye precursors (primary intermediates and couplers) and ammonia. This solution is invariably a mixture of precursors, sometimes as few as 3, usually 5−6, with a maximum of 10−12. The second component is a stabilized hydrogen peroxide solution. The two are mixed immediately before use to give a pH of 9.5 required for the coloration process. The mixture is initially applied near to the hair roots for 20−40 min to allow exposure to undyed new growth, followed by application to the rest of the hair, before rinsing with water.

Scheme 6. Oxidation of *p*-Phenylenediamine to the Diimine



22 23 24

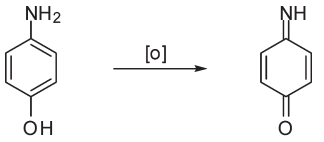
The first step in oxidative hair dyeing involves oxidation of the primary intermediate with alkaline hydrogen peroxide. The nature of the specific reactive species involving hair coloration with *p*-phenylenediamine (**22**) is still under debate. *P*-benzoquinonediimine (**23**) (Scheme 6) has been proposed.[94] Alternatively, its conjugated acid **24** has been proposed in the pH range 7−10, with the pK_a of **24** being 5.75.[95,96] This conclusion is supported on the basis that the diiminium ion is much more electrophilic than the diimine.[97] Further, *N*,*N*-dialkyl-*p*-phenylenediamine derivatives, which are capable of forming a diiminium ion but not a diimine, can act as primary intermediates in oxidative hair dyeing. In contrast, *p*-benzoquinonimine (**26**) has been identified as the reactive species from *p*-aminophenol (**25**) (Scheme 7).[98]

A mechanism involving a Wurster salt may also be considered. The Wurster salt **27** may be obtained from *p*-phenylenediamine by electrochemical oxidation in buffered media by the mechanism illustrated in Scheme 8.[99] However, the stability of the radical decreases rapidly above pH 6, which further reinforces the concept of diiminium ion **24** as the active species.

In the absence of couplers, the oxidation of compounds **22** and **25** lead to trinuclear species, the so-called Bandrowski's bases,[100−102] **32a** and **32b**, respectively (Scheme 9), which react further to give a dark brown/black polymer. Oxidation of **22** with hydrogen peroxide also forms *p*-nitrosoaniline and 4,4′-diaminoazobenzene. However, it is believed that Bandrowski's bases are not formed in the hair.[103] Primary intermediates are weaker electrophiles than couplers so that there is almost no self-coupling in

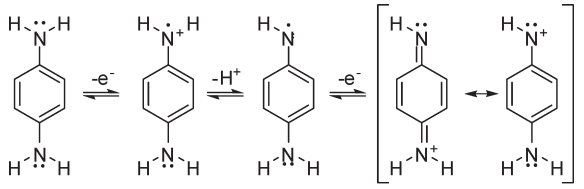
dx.doi.org/10.1021/cr1000145 |*Chem. Rev.* 2011, 111, 2537–2561

Scheme 7. Oxidation of *p*-Aminophenol to the Imine



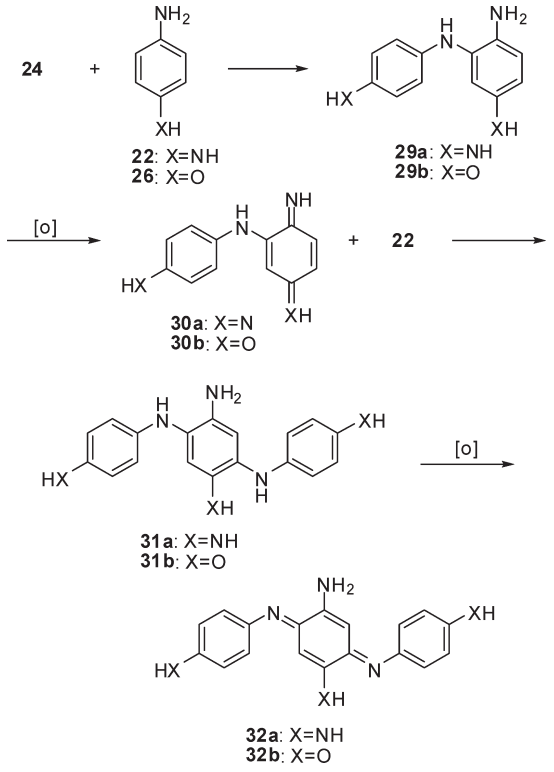
25 26

Scheme 8. Oxidation of *p*-Phenylenediamine Involving Wurster Salts



22 27 28 24

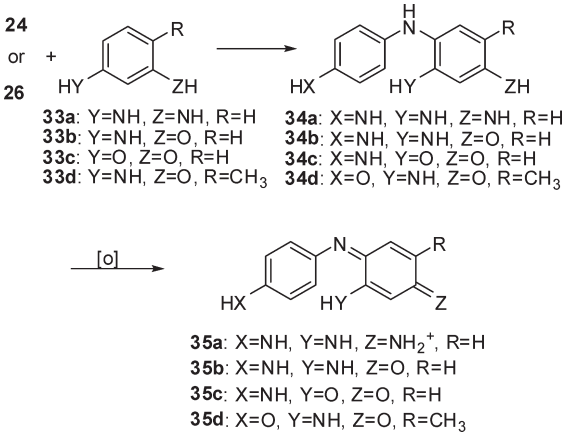
Scheme 9. Self-Coupling Reaction of *p*-Phenylenediamine (X = NH) and *p*-Aminophenol (X = O)



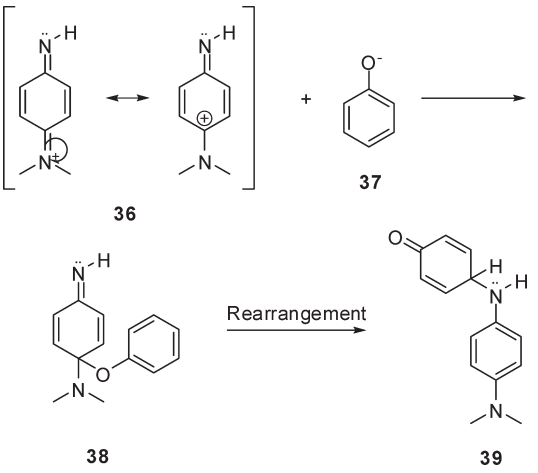
their presence, with the reaction between **22** and a standard coupler being 10^4-10^5 times faster than the reaction to produce **32a**. The reactive species (**24** or **26**) generally attack the coupler preferentially para to an amino or hydroxy group, forming leuco compounds **34a**−**34d**, which further oxidize to give dinuclear indo dyes **35a**−**35d** (Scheme 10).

A model for the oxidative coupling reaction of *N*,*N*-dimethyl-*p*-phenylenediamine with phenol has been examined theoretically

Scheme 10. General Pathway for the Formation of Dinuclear Indo Dyes



Scheme 11. Proposed Mechanism for the Oxidative Coupling Reaction of *N*,*N*-Dimethyl-*p*-phenylenediamine with Phenol



using ab initio molecular orbital and density functional theory methods.[104] On this basis, a mechanism for formation of **34a**−**34d** by a [5,5]-sigmatropic rearrangement (Scheme 11) was proposed. Frontier orbital calculations suggest that negative charge is localized on oxygen in **37** whereas positive charge is localized on the carbon atom of the diiminium ion, as exemplified in the mesomeric structure **36**. Thus, it is proposed that reaction takes place with phenol initially to generate intermediate **38**, which undergoes rearrangement to leuco compound **39**. This mechanism has yet to be verified experimentally.

In the case where R = H (see Scheme 10), a further molecule of **24** or **26** may undergo 1,4-addition to the dinuclear indo dyes to form trinuclear indo dyes **41a**−**41b** (Scheme 12). Further reactions to generate polymeric structures may take place, but this feature is as yet not fully understood.

Most reactions of the primary intermediates with the various couplers follow variants of the mechanisms illustrated in Schemes 10 and 12. In particular, at pH > 7, **22** reacts (via **24**) by electrophilic attack at the 4-position of *m*-phenylenediamine (**33a**), in its neutral form (pK_a = 5.0), to produce the dinuclear species, which undergoes rapid oxidation to a blue dye in the hair,

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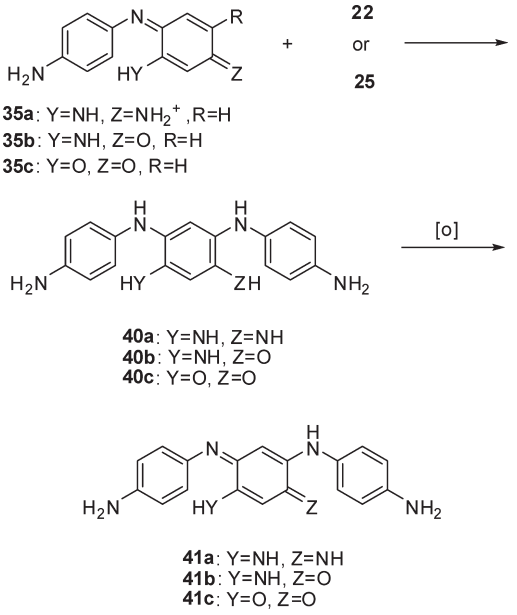
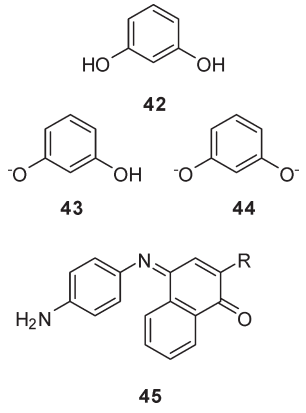
Scheme 12. Proposed Pathway for the Formation of the Trinuclear Indo Dyes



as its conjugate acid **35a** (at pH 7).[105,106] A second molecule of **22** can then undergo addition (Scheme 12) to form violet−blue trinuclear species **41a**.[107] If the *m*-phenylenediamine coupler carries an electron-donating substituent at the 4-position, intramolecular cyclization of the dinuclear species leading to the formation of phenazine-2,8-diamine, which provides an undesirable reddening of the color, is prevented. The reaction between **22** and *m*-aminophenol couplers is similar. At pH > 8, *m*-aminophenol (**33b**) reacts as the phenoxide ion to form magenta dye **35b**, which may undergo further reaction with **24** to produce trinuclear indo dye **41b**, giving a dull brown color. This last reaction may be blocked by substitution in the 6-position (R ≠ H in Scheme 10), e.g., with a methyl group as in **33d**, to avoid the dull coloration. The coupling of **22** with resorcinol **42**, probably the most commonly used coupler, involves reaction of **24** with either monoanion **43** or dianion **44** depending on the pH, to form the dinuclear indo dye, which undergoes oxidation to magenta dye **35c**. Further reaction with **24** gives the trinuclear green pigment **41c**.

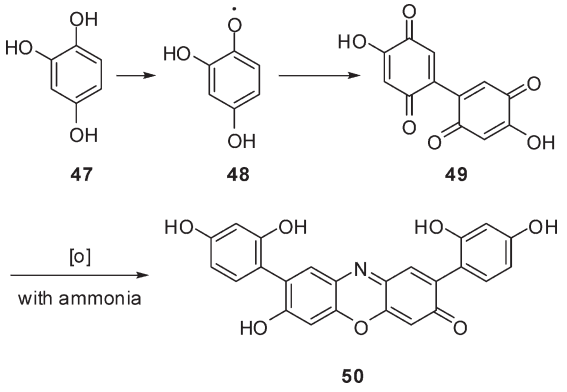


Naphthol derivatives react similarly; **24** reacts with the anion of α-naphthol at the 4-position to form bluish-purple dye **45**. With *N,N*-dialkylated-*p*-phenylenediamines, the dye formed is pure blue, a bathochromic shift resulting from increased donor strength of the amino group. Reaction may either terminate at this stage or proceed by addition of a further molecule of **24** to form a trinuclear indo dye. *p*-Aminophenol reacts with *m*-aminophenol couplers, para to the hydroxy group, e.g., in the case of 6-methyl-3-aminophenol, to form orange−red dye **35d**.

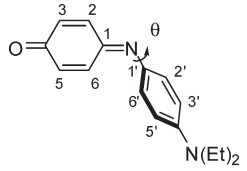
Formulated hair dye products contain mixtures of primary intermediates and couplers. Thus, the hair color will depend on competing reactions between the various dye precursors inside the fiber, influenced by factors such as concentrations, diffusion rates, redox potentials, and pH.[108] Predictions based on kinetics have been consistent with the colors obtained, at least qualitatively, implying that the relative reactivities of reactants are more important than their relative concentrations. Nevertheless, in such a complex system, there remains some uncertainty as to whether the rates of coupling inside the hair fiber are kinetically controlled or diffusion-controlled. Interestingly, primary intermediate oxidation is observed to be much faster inside the hair fiber than in an aqueous dyebath. An explanation has been proposed involving diffusion of hydrogen peroxide into the hair followed by its decomposition to form oxygen, which is considered as much more reactive toward the primary intermediates.[109] In increasing order of redox potentials, *p*-aminophenol (**25**) and its derivatives are oxidized before *N,N*-disubstituted *p*-phenylenediamines, in turn oxidized more readily than *p*-phenylenediamine (**22**). Coupler selection is critical in hair dye formulation. For example, if an auburn shade is required from a composition containing **22** and **25**, the most reactive coupler is chosen so as to ensure formation of a red dye, since **25** will undergo oxidation first and then react with this coupler to give the desired red color, before dyes resulting from coupling with **22**. The substitution pattern in the dye precursors plays an important role in determining not only their reactivity but also the final color. Electron-donating groups in the primary intermediates increase the initial rate of oxidation but decrease the reactivity of electrophilic species toward the couplers. Electron-donating groups enhance the reactivity of couplers. In general, electron-donating groups in the coupler provide a hypsochromic shift of the color of the resulting indo dye, while electron-withdrawing groups give a bathochromic shift. The opposite substituent effect is observed with primary intermediates. However, color−structure relationships in the indo dyes are complex. X-ray crystallographic studies of indo dyes of this type have revealed their nonplanarity.[110] In some cases, less planar compounds were bathochromically shifted compared with more planar derivatives. Studies using AM1 (Austin model 1) and INDO/S (intermediate neglect of differential overlap) molecular orbital methods have predicted that increasing the angle ($0 < \theta < 90°$) between the two rings of dye **46** gives rise to bathochromic wavelength shifts and a decrease in oscillator strengths (f_{osc}),[111,112] a parameter related to the molar extinction coefficient and, hence, the color intensity.

Thus, the color of the indo dyes formed is also a function of molecular conformation. This is relevant in oxidative hair dyeing because the dyes are formed inside the hair fiber in a cross-linked matrix in which intermolecular forces may cause the dye to adopt a particular conformation. This may explain an observation in the course of studies on the photochemical properties and physical modifications of permanent hair dyes, that the same aminoindamine

Scheme 13. Auto-oxidation of 1,2,4-Trihydroxybenzene (47)



synthesized in the laboratory and inside the hair gave different UV−visible spectra.[113]



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In addition to its impact on the swelling of the hair fiber, pH can also influence the rate of color formation from a particular coupling reaction, an effect dependent on the pK_a values of the reactants involved. In a typical oxidation dye composition with **22** as primary intermediate and three couplers, resorcinol, *m*-aminophenol, and *m*-phenylenediamine at pH 9−9.5, the couplers react at similar rates. However, lowering the pH by one unit increases the rate of the reaction with *m*-phenylenediamine relative to resorcinol and *m*-aminophenol. On the other hand, increasing the pH by one unit increases the relative rate of reaction with resorcinol. Thus, pH may be used as a tool to adjust tone or depth.

Auto-oxidative hair dyeing involves the oxidation of dye precursors by oxygen in air without additional oxidant.[5] This technology is based on dye precursors such as 1,2,4-trihydroxybenzene (**47**), 2,4-diaminophenol, 2-methoxy-*p*-phenylenediamine, or 3,4-dihydroxyaniline. In contrast to traditional oxidative dyeing, the hair is not lightened and so the system is often targeted to color gray hair. In this way, precursor **47** gives a medium-brown hair color. The first step is oxidation of **47** to form semiquinone radicals **48**,[114] which react further to form diphenylquinones **49** by a carbon−carbon coupling reaction. Diphenylquinones **49** are very reactive and may play an important part in the formation of the brown pigment. If the reaction is carried out in the presence of ammonia, pigments related to orcein dyes[115] **50** are formed (Scheme 13).

6. SEARCH FOR NEW HAIR DYE PRECURSORS

Over the years, countless numbers of dye precursors have been claimed in patents as fulfilling the requirements for oxidative hair dyeing, aiming to address issues associated with toxicology and coloristic performance.[8] The research intensity has produced individual successes, although most of the compounds in current commercial dye formulations remain those used for decades.

A range of derivatives of compounds **22** and **25**, *N*-substituted or *N*,*N*′-disubstituted with groups such as trifluoroalkyl,[116] ether,[117] alkylsulfonamides,[118] aromatic,[119] heterocyclic,[120−123] heteroaromatic,[123−126] and amino acids,[127] have been reported. A similar strategy is evident with *m*-phenylenediamine couplers.[128−131] This approach is claimed to have provided improved lightfastness, for example, with 2-methyl-5-*N*-substituted-aminophenol derivatives,[132−136] and has also targeted a color shift to longer wavelengths of the dinuclear indo dyes formed, giving violet to blue shades.[137−140] The bathochromic shift, a consequence of the increased donor strength from the *N*,*N*-disubstitution in this case, can also be achieved by introduction into the coupler of powerful electron-withdrawing groups, such as the cyanine auxochromes.[141] Derivatives of 2-(sulfonylamino)phenol are claimed as couplers capable of generating bright, intense blond colors with good resistance toward washing and light.[142]

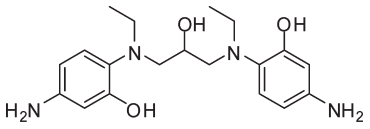
Benzene ring substitution in compounds **22** and **25** has been used in attempts to address toxicological and coloristic issues. 2-Substituted *p*-phenylenediamines[143−161] and *p*-aminophenols[162−172] have been extensively claimed. 3-Substituents, although less extensively reported, have also been highlighted as improving performance and coloristic properties of *p*-aminophenol derivatives, giving good, even coverage of various hair types.[170,173−178] 4-Substitution by halogens[179,180] and alkoxy groups[181] and polysubstitution by halogens[182] in *m*-aminophenol couplers have been proposed as alternatives to *N*,*N*-disubstitution to enhance lightfastness. *M*-phenylenediamine couplers with electron-donating substituents in the 4-position have been aimed at avoiding a slow cyclization reported to produce red species rather than the desired blue color.[183−187] In contrast, the strong reddish-blue color achieved with trialkoxy-*m*-phenylenediamines[188] or dialkoxy-*m*-phenylenediamines[189−191] has been reported as desirable. Ring substitution, optionally combined with *N*-substitution,[192−201] may also cause a bathochromic shift and modify color intensity. 2,4-Disubstituted-*m*-phenylenediamines have been investigated to address the relatively low intensity of the blue color from *m*-phenylenediamine couplers.[202−204] Of particular interest is a series of patents which make use of thioalkylated-*m*-phenylenediamines, appearing to associate the chemistries of hair coloring and styling, and which claim improved washfastness and lightfastness.[205−212] *M*-Aminophenol couplers substituted at the 2-position with aromatic,[213] heteroaromatic,[214] or acrylamide[215] groups have been reported.

Commonly, formulations to achieve gold shades employ the addition of semipermanent nitro dyes. *O*-Phenylenediamines, as alternatives to the *p*-isomers, have been suggested as offering the potential to fulfill the need for primary intermediates, which can produce the required yellow and orange shades with suitable couplers. However, this type of compound leads to poor lightfastness. In attempts to develop more suitable primary intermediates to meet the color and technical requirements, new *o*-aminophenol derivatives[216,217] have been claimed. However, when used alone, they do not appear to meet the requirements of oxidative hair coloration.

Relatively recent patent literature reveals considerable interest in the conversion of nonionic dye precursors into cationic salts, a feature which enhances dye uptake by the hair fiber, for example, using *N*-methylimidazole[218−220] or alkylating agents,[221−224]

dx.doi.org/10.1021/cr1000145 |*Chem. Rev.* 2011, 111, 2537–2561

although this concept is not new.[225,226] Examples of couplers modified as cationic salts include naphthols,[227,228] 4-substituted-*m*-phenylenediamines,[229,230] *o*-sulfonamidophenols, and *m*-aminophenols,[231] especially 2-methyl-5-*N*-substituted-aminophenol derivatives.[232,233] A *m*-aminophenol with an *o*-substituent containing a cationic group is claimed to give blue colors with suitable primary intermediates.[234] Cationic *o*-phenylenediamine derivatives are claimed to provide enhanced depth of penetration into the fiber and also reduced photodegradation of the dye formed in the hair fiber.[235,236]



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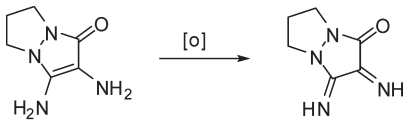
With the commercial introduction of 2-hydroxy-1,3-bis-(*N*-2-hydroxyethyl-4-aminophenylamino)propane (**51**) as a primary intermediate, bridged bis-*p*-phenylenediamine derivatives based on 1,3-bis(*N*-(4-aminophenyl)-*N*-(2-hydroxyethyl)amino)propan-2-ol[237] have been claimed. A similar concept has been applied to *o*-phenylenediamine.[238,239] *N*-methylimidazolium salts have been introduced into the bridge leading to new primary intermediates based on **22** and **25**,[240] with the cationic character counterbalancing the effect of increased molecular size in facilitating penetration into the fiber. A similar approach applied to couplers has led to bis-*m*-phenylenediamines with a cationic bridge,[241] bis-(2,4-diaminophenyl)-alkanes,[242,243] bis-(2,4-diaminophenyl)-alkanols,[244] and others.[245−249] Because of increased molecular size, these couplers give improved shampoo fastness, with suitable primary intermediates, on damaged hair.

Heterocyclic dye precursors have been extensively considered as alternatives to carbocyclics. With the commercial introduction of 2,4,5,6-tetraminopyrimidine as a primary intermediate, other tetraminopyrimidines,[250−253] triaminopyrimidines,[254] and triamino-pyrimidinone derivatives[255] have been claimed. Renewed interest in pyridine derivatives is indicated by claims as primary intermediates[256,257] and as couplers.[258−262] Recently, interest has been extended to novel heterocyclic systems, exemplified by primary intermediates based on 4-amino-2,2-dimethyl-2,3-dihydrobenzofuran-7-ol[263,264] and 1,4,7-triazonane.[265] The range of heterocyclic couplers patented include quinolines, benzoxazines and benzothiazines,[266] benzotriazoles,[267] hydroxybenzofurans,[268] benzimidazoles,[269,270] and 1,2,3,4-tetrahydroquinoxalines.[271]

Pyrazole chemistry appears to be showing promise in the search for new primary intermediates, derived from the claim that *N*-arylpyrroles may decrease the dermatological allergenic risk associated with **22**.[272] Patents describe 3,4-diamino-,[273−275] 4,5-diamino-,[276−281] and 3,4,5-triaminopyrazoles[282] as primary intermediates, as well as cationic analogues.[283] The main aim is to provide nonfading red shades on hair, with an improved toxicological profile, with the potential to replace **25** and to obtain brighter colors than with pyrimidine or pyridine primary intermediates. Subsequent developments include primary intermediates based on related heterocycles such as pyrazolo[1,5-*a*]-pyridines,[284] pyrazoloazoles,[285] pyrazolo[1,5-*b*]-1,2,4-triazole, pyrazolo[3,2-*c*]-1,2,4-triazole,[286] pyrazolo[1,5-*e*]tetrazole, pyrazolo-[1,5-*b*]pyrazole and imidazo[1,2-*b*]pyrazole, pyrazolo[1,5-*e*]-

Scheme 14. Oxidation of 52 to the Quinone Diimine

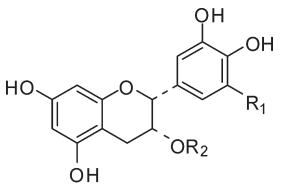


52 **53**

1,2,3-triazole, and pyrazolo[1,5-*a*]pyrimidines,[287−289] with the last group also as cationic analogues.[290] Bridged pyrazoles have also been claimed.[291] A successful outcome of this research is demonstrated by the recent commercial launch by L'Oreal of primary intermediates based on derivatives of 2,3-diamino-6,7-dihydropyrazolo[1,2-a]pyrazol-1(5H)-one (**52**) in its Rubilane range.[292−296] This new range of dihydropyrazolones is claimed to provide a variety of coloristic advantages, such as improved intensity, chromaticity, and aesthetic qualities, with good resistance to shampooing, light, perspiration, and permanent waving. They are also claimed to undergo oxidation, through a similar mechanism as with **22** to generate the corresponding quinone diimine (Scheme 14), at neutral pH, which introduces the benefit of minimizing hair damage.

In parallel, aminopyrrole derivatives have also been described as couplers.[297] Couplers have been patented based on 4,5-methylenedioxyphenol,[298,299] bispyrazole aza compounds,[300] pyrazoline-3,5-dione,[301,302] 3-aminopyrazoline,[303] pyrazolo[1,5-*b*]-1,2,4-triazole, pyrazolo[3,2-*c*]-1,2,4-triazole, pyrazolo[1,5-*e*]tetrazole, pyrazolo[1,5-*b*]pyrazole, pyrazolo-[1,2-*a*]pyrazol-1(5H)-one,[292] imidazo[1,2-*b*]pyrazole, pyrazolo[1,5-*e*]-1,2,3-triazole,[304,305] pyrazolo[3,4-*d*]thiazoles,[306] pyrazolo[5,1-*c*]-1,2,4-triazoles,[307] pyrazolo[1,5-*a*]pyrimidi-5-one, and pyrazolo[1,5-*a*]pyrimidi-7-one.[308,309] Other novel heterocycles claimed to be suitable as couplers in oxidative hair dyeing include derivatives of 4-phenylpyrrolo[3,2-*d*]-oxazoles,[310] imidazo[5,1-*b*]thiazol-3(2H)-one, thiazolo[3,2-*b*][1,2,4]triazol-6(5H)-one,[311] imidazolo[3,2-*a*]imidazole, imidazolo[1,2-*b*]-1,2,4-triazole and imidazolo[2,1-*c*]-1,2,3-triazole,[312] cationic indolizine derivatives,[313] hydroxyimidazo[1,2-*a*]pyridines, and aminoimidazo[1,2-*a*]pyridines.[314] A number of indole compounds have been examined as couplers, conceivably influenced by recognition of their involvement in the biosynthesis of melanin. 6- and 7-hydroxyindole derivatives,[315] used in combination, with aromatic *p*-diamines, have been claimed to give particularly good resistance toward light and washing. 4-Hydroxyindole derivatives have also been claimed, modified by *N*-substitution with hydrophilic groups[316,317] and as cationic analogues.[290,318] Derivatives of 4-, 5-, 6-, and 7-aminoindole[319,320] and *N*-substituted analogues[321] have also been reported as couplers, demonstrating similar properties to the hydroxyindoles. N-substituted 4-hydroxyindolines[322,323] have been investigated as couplers. 5,6-Dihydroxyindoline[324] and 2-iminoindoline[325] couplers are claimed to produce intense blond and brown shades with conventional primary intermediates. Indazolamine couplers[326] have recently been reported to produce violet−blue colors with **22** and yellow to red colors with **25**, although similar compounds had been patented for use in oxidative hair coloration some 20 years previously.[327] Compounds based on 1H-perimidine and 2,3-dihydroperimidine, structurally related to perylene pigments, are

claimed to give black dyeings from appropriate hair color formulations.[328,329]



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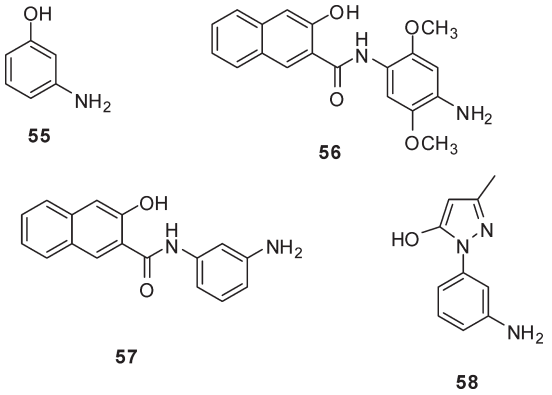
Research to address technical and toxicological issues associated with resorcinol, a conventional coupler, have led to patents on derivatives such as mono- and dialkyl,[330] 4-,[331] 5-,[331,332] and 6-substituted[243] resorcinols, and compounds such as diresorcyl sulfide, sulfoxide, and sulfone.[333] However, resorcinol continues to be accepted in commercial hair dye formulations, which suggests that these developments have not offered significant advantages. A natural plant-derived compound **54**, with some of the structural features of resorcinol, has been claimed as a coupler, giving olive-brown colors. *O*-Aminophenols have also received recent attention, especially *o*-carbamoylphenol derivatives as cationic salts.[334] Inspired by the concept of compound **51**, bis-*o*-aminophenol compounds bridged by an imidazolium group are claimed to impart blond colors.[335]

Patents have also been issued on new color development chemistry, avoiding the use of hydrogen peroxide and alkali. The bleaching effect of the traditional oxidizing system degrades the hair fiber, rendering it coarse and fragile. An electrochemical method has been claimed to oxidize dye precursors,[336] and enzymatic oxidation systems have also been claimed.[337] Although such systems are capable of oxidizing the primary intermediates, they are not able to perform the function of lightening hair. Fluorescent compounds have been investigated for their potential to lighten hair,[338,339] including bis[2-(4-(dimethylamino))styrylpyridinium] derivatives.[340]

7. ALTERNATIVE PROCESSES FOR PERMANENT HAIR DYEING

7.1. In Situ Reactions

7.1.1. Formation of Azo Colorants. Azo dyes and pigments are by far the most important commercial colorants, providing virtually a full range of bright, intense hues and reasonable to very good technical performance. They are inexpensive, synthesized at ambient temperature in water from commodity starting materials. Thus, a permanent hair dyeing process based on synthesis of insoluble azo colorants within the hair fiber presents an attractive concept. The first such process involved reaction of stabilized diazonium salts with coupling components, similar to the traditional couplers used in oxidative hair coloration.[341] As an example, 4-(*N*-phenyl)aminobenzenediazonium tetrachlorozincate with α-naphthol gives a strong black color on hair. The procedure involved contact of an aqueous alkaline coupling component solution with hair for 20 min, addition of aqueous diazonium salt solution, and then another 20 min for the in situ azo coupling. A limited range of brown to black shades was achieved. Subsequently, the process was improved using coupling components with a higher affinity for hair than the naphthols,[342,343] also providing an extended shade range. Beyond this patent series, there is limited evidence of further development. Cationic coupling components have been claimed to improve uptake.[344] New stable diazonium salts have been proposed, including 2,5-dimethoxy-4-benzoylaminophenyldiazonium chloride[345] with amines, commonly used as couplers in oxidative hair coloration, as coupling components. The lightening of the hair was addressed by incorporation of an oxidant, generally hydrogen peroxide, into the formulation.[345,346] A method has been reported which forms oligomeric or polymeric azo colorants in the hair fiber,[347,348] giving dyeings with very good washfastness and minimal hair damage. Diazonium salts resulting from the reaction of aromatic amines, such as **55**−**58**, with aqueous sodium nitrite and hydrochloric acid, are applied to the hair, typically at pH 3−4. After 2−10 min, increasing the pH to 8−9 induces a self-coupling reaction, likely to produce polymeric species. The colors obtained are copper with **55**, blue with **56**, red with **57**, and orange with **58**. However, such processes do not appear to have been commercialized, with one negative issue being the potential risk of explosion during storage of diazonium salts.

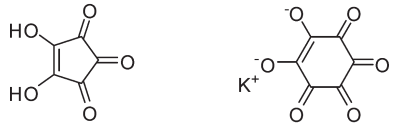


7.1.2. Formation of Methine and Azomethine Colorants

7.1.2.a. Condensation of Amines with Carbonyl Compounds. A significant issue in oxidative hair dyeing is the substantial hair damage from the use of strongly alkaline conditions and oxidizing agents. Attempts have been made to develop dyeing systems that avoid these conditions yet give intense coloration and good fastness properties. One such system is based on reactions of amines with aldehydes or ketones, using small molecules that can penetrate easily into the fiber and then undergo condensation to form methine or azomethine dyes, which become trapped inside the hair. The two components may be applied separately or mixed just before use. There are certain chemical similarities with the oxidative process, but neither hydrogen peroxide nor ammonia are needed for color development. Coloration of blond hair was reported by treatment with aqueous solutions, emulsions, or dispersions of equal parts of one or more dialdehyde and the amines for a few minutes, followed by warm water rinsing.[349] Brown or black shades were obtained using amines such as *p*-phenylenediamine and mono-, di-, or triethanolamine with phthalaldehyde isomers, with the primary amino group reacting with the aldehyde to form imines (Schiff bases). A further development used benzaldehyde and cinnamaldehyde derivatives and incorporated a metal salt to minimize light-induced fading of the dyed fiber,[350] a technique similar to textile mordanting.[351] In this way, a wider color range was

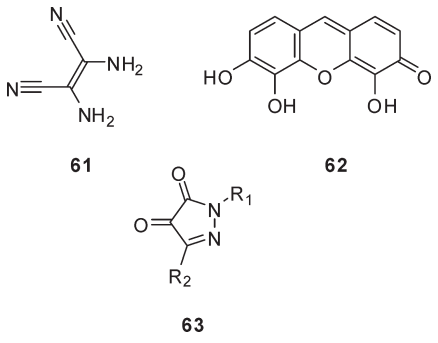
dx.doi.org/10.1021/cr1000145 |*Chem. Rev.* 2011, 111, 2537–2561

obtained. Bleached hair may be dyed with 5-aminoindole and 4-*N*,*N*-dimethylamino derivatives of cinnamaldehyde or benzaldehyde to provide brown and red shades.[352] With isatin, yellow to red shades are reported on bleached hair.[353] A series of further patents report the reaction of isatin at weakly acidic pH with aminoindoles,[354] aromatic diamines, di-, tri-, or tetrasubstituted aminophenols, bisphenylalkylenediamines,[355] aminopyridines,[356] and aminopyrimidines[357] to give yellow to purple shades on natural gray hair. Unsubstituted[358] and *N*-substituted isatin[359] and its 5-sulfonic acid[360] are reported to react with aromatic amines and amino acids to provide yellow to purple−red hair colors. 3-Aminoisoindolone is reported, in combination with *p*-phenylenediamine, *p*-aminophenol, aminopyridine, diaminopyrazolo[1,5-*a*]pyrimidine, aminopyrazoline, aminoindazole, and aminoindole derivatives, to produce yellow to violet shades.[361,362] Benzoquinone derivatives, particularly *o*-benzoquinone,[363] croconic acid (**59**), and potassium rhodizonate (**60**),[364] have also been proposed as appropriate carbonyl compounds.



59 **60**

In a straightforward dyeing method, the aldehyde solution is applied to hair at room temperature, and after 5 min, the amino compound solution is applied. After 20 min at 40 °C, the hair is rinsed. *p*-Phenylenediamine, *o*-aminophenols, diaminomaleic acid dinitrile (**61**), and derivatives of 4,5,6-trihydroxy-3H-xanthen-3-one (**62**) may be used to provide shades from blond to red and violet.

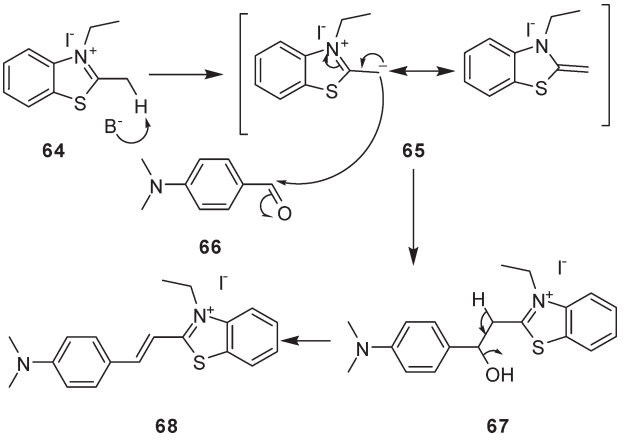


61 **62**

63

Using a similar process, a series of nitroarylamines and cyanoanilines are reported to condense with *o*-benzoquinone, 4,5-dihydroxycyclopent-4-ene-1,2,3-trione **59**, or 5,6-dihydroxycyclohex-5-ene-1,2,3,4-tetraone **60** to give yellow−orange to reddish-brown shades.[364] Pyrazolin-4,5-dione **63** is reported to give uniform dyeings of reddish-orange to violet shades.[365−367] On the basis of similar chemistry, a range of hydrazones, such as derivatives of 2-benzothiazolinone hydrazone[368] and of thiazolonehydrazone,[369,370] are claimed to produce a wide color range by reaction with quinonoid compounds. Amino compounds containing cationic groups have been used to promote uptake of the reactive species by the fiber. Formulations reported include isatin and an aromatic amine containing either an aliphatic[371] or a heterocyclic cationic group[372] to give shades from yellow to magenta on bleached hair. A further development of this chemistry involves *p*-benzoquinonemonoimine derivatives, protected as the *o*-(methylsulfonyl)oxime, which is deprotected with alkali, to allow reaction with amines and phenols to generate, in this case, indo dyes with colors ranging from yellow to violet.[373]

Scheme 15. In Situ Reaction of 3-Ethyl-2-methylbenzothiazolium Iodide with 4-Dimethylaminobenzaldehyde by a Knoevenagel Condensation

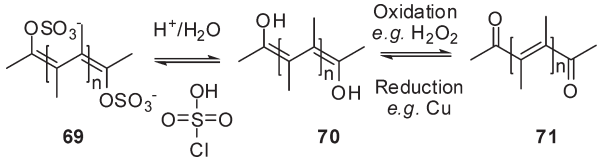


64 **65** **66** **68** **67**

7.1.2.b. Knoevenagel Condensation. An interesting development of the hair dyeing system described in the previous section involves formation of methine or azomethine dyes by in situ Knoevenagel condensation. This system similarly does not require an oxidant and utilizes a cationic species as one of the reagents. The acidic hydrogen of a heterocyclic quaternary salt, exemplified by 3-ethyl-2-methylbenzothiazolium iodide (**64**) in Scheme 15, is readily removed by a base, e.g., monoethanolamine, to generate an enamine **65**, which undergoes an addition reaction with a carbonyl compound, such as 4-dimethylaminobenzaldehyde (**66**). The methine dye **68** is formed by elimination of water from intermediate **67**. A wide range of cationic salts are suitable, and the carbonyl compounds also include 1,4-naphthoquinone and isatin, to provide mainly yellow to red shades, whereas some compositions are claimed to give violet−blue shades on natural gray hair.[374] Similar cationic salts used with benzaldehyde derivatives are claimed to give orange to purple−red shades on hair.[375,376] A series of 1,2-dihydropyrimidinium salts used in combination with a variety of reactive aromatic carbonyl compounds is claimed to impart hair colors ranging from yellow−brown to blue.[377] Piperidine is claimed as a color intensifier, acting as a base to remove the acidic β-hydrogen. Similarly, the use of 1,2,3,3,5-pentamethyl- and some 5-substituted-1,2,3,3-pentamethyl-3*H*-indolium iodides with benzaldehyde derivatives and sodium acetate is reported.[378] An advantage claimed for this composition is the ability to remove color completely at any desired subsequent time using aqueous sodium sulfite at pH 5.

Relatively recent patent activity indicates significant interest in this technology. Dyes of the type formed have been proposed as semipermanent products for direct application to hair since they provide bright, intense colors.[379,380] However, they tend to show inferior fastness properties compared to other chemical classes, and this may be one reason why this permanent hair dyeing system has not yet reached the market.

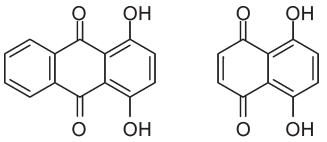
Scheme 16. Process of Solubilized Vat Dyeing



7.2. Latent Colorants

7.2.1. Leuco Vat Dyeing. Vat dyes represent an important dye class for coloration of cellulosic textile fibers such as cotton. They are applied to the fiber via the reduced, or *leuco*, form, which is then reoxidized in the fiber. Solubilized vat dyes are sulfate esters of the leuco vat dyes.[381] The dyes were originally developed for protein fibers, wool, and silk, so that the strongly alkaline conditions required for vatting might be avoided, although they have ultimately proved more important for cellulosic fibers.[382] Two disadvantages of conventional oxidative hair dyeing are that it does not readily produce bright red and yellow colors and, when carried out at low pH to reduce hair damage, the colors are dull and drab. It has been envisaged that solubilized vat dyes might address these issues, at the same time giving the excellent fastness to light and washing that is characteristic of vat dyes. Solubilized vat dyeing of hair has been reported.[383] As illustrated in Scheme 16, the process involves application of the solubilized vat dye **69** to hair, followed by low pH hydrolysis to give leuco vat dye **70**, which is then oxidized to generate the vat pigment **71** trapped inside the hair fiber. The technology is compatible with conventional oxidative hair coloring in that it uses hydrogen peroxide, or ammonium persulfate, as oxidizing agent. The solubilized vat dye can also generate the pigment by irradiation with light.

Leuco derivatives of indo dyes have also been applied to hair. Indo dyes, the products from reaction of conventional oxidative coupling of primary intermediates, such as compounds **22** or **25**, with a coupler such as *m*-phenylenediamine or *m*-aminophenol, are reduced by sodium dithionite to give the leuco form of the benzoquinoneimine **72**, which is neutralized with acetic acid to generate the stable diphenylamine derivatives **73**, as exemplified in Scheme 17. These colorless compounds are applied to hair and oxidized in situ. Numerous derivatives based on compound **73** have been patented for this process.[384−391]

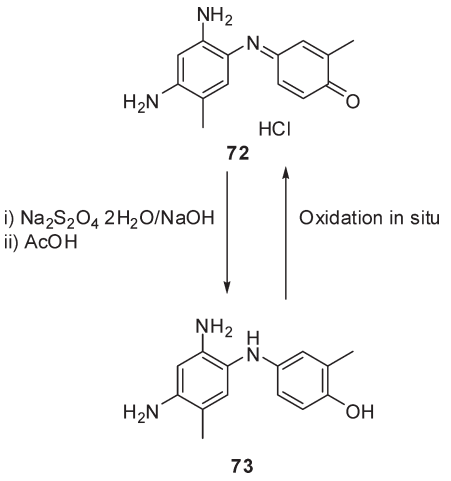


74 **75**

Leuco derivatives of quinizarin (**74**) and naphthazarin (**75**) have been investigated for permanent hair coloration using air oxidation. Leuconaphthazarin was observed to dye hair from an aqueous medium, without the need for an additional oxidant, to give a reddish-purple shade. However, leucoquinizarin showed low dyeability.[392] Leuco derivatives of *N*-phenylaminopyrazole, which may be converted to dyes of high intensity and good fastness properties by oxidation, have been claimed.[393]

7.2.2. Latent Pigment Technology. In 1995, Ciba introduced the concept of latent pigment technology based on a

Scheme 17. Process of Hair Dyeing with Leuco Forms of Indo Dyes



pigment precursor, the *latent pigment*, which is soluble or homogeneously dispersible as a dye in the application medium.[394−396] Following a physical or chemical treatment, the pigment is generated quantitatively in situ. This novel approach to pigmentation is designed to reduce the time, cost, and effort to comminute the crude pigment to the desired particle size and shape. Ciba has patented the use of this technology for porous materials, especially wood,[397,398] with hair mentioned as a material that might conceivably be pigmented in this way. However, the original latent pigments generally required high application temperatures, inappropriate for hair coloration. The design of a pigment precursor that would penetrate the hair and, by subsequent chemical and/or physical treatment, regenerate the pigment trapped within the fiber represents an interesting concept for permanent hair coloration.

A process for hair dyeing uses indican (**76**) from the leaf used to provide natural indigo.[399,400] A formulation containing extracted indican and a separate formulation containing a β-glucosidase enzyme are applied to hair at 40−45 °C for 30 min. Compound **76** is hydrolyzed by the β-glucosidase to indoxyl (**77**), which undergoes rapid air oxidation in hair to form indigo (**78**) (Scheme 18). The use of indigo precursors 5-bromo-4-chloro-3-indolyl-β-D-galactoside and the corresponding glucopyranoside with appropriate enzymes are also described as coloring hair light blue and violet−blue, respectively.[401] The concept of latent pigment technology applied to hair coloration has been patented on the basis of the derivative **79**,[402,403] which cleaves at room temperature after 30 min to give indigo by base-catalyzed hydrolysis with triethanolamine (Scheme 19).[404,405]

A similar concept has been used to enhance the solubility and the storage stability of direct dyes in hair dye formulations by transformation into enzymatically labile dye precursors, e.g., **81**, which, prior to hair dyeing, are cleaved with a suitable enzyme to generate a dyeing mixture. This latter is applied at 37 °C for 30 min to give a deep orange color due to **80** on hair (Scheme 20).[406]

Pigments generated within hair using technologies of this type are likely to form as nanoparticles. It has been postulated that the application of nanotechnology in human hair dates back thousand of years, when ancient Greek and Roman civilizations grew lead sulfide nanocrystals inside hair fibers to give a black

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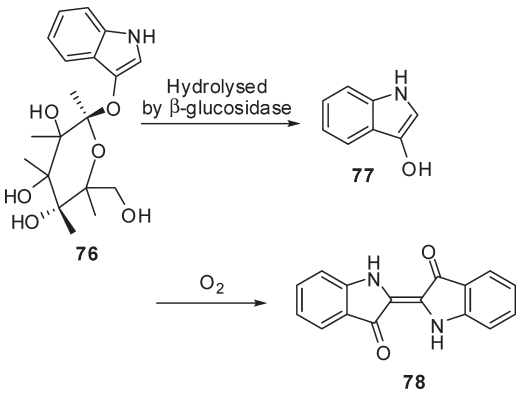
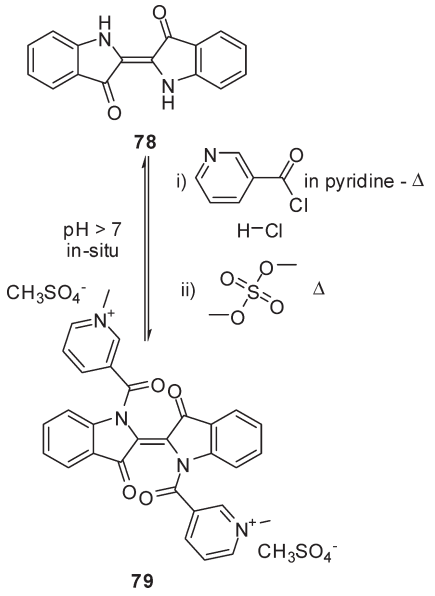
Scheme 18. Formation of Indigo from Indican With a β-Glucosidase Enzyme



Scheme 19. Latent Pigment Technology Applied to Hair Coloration

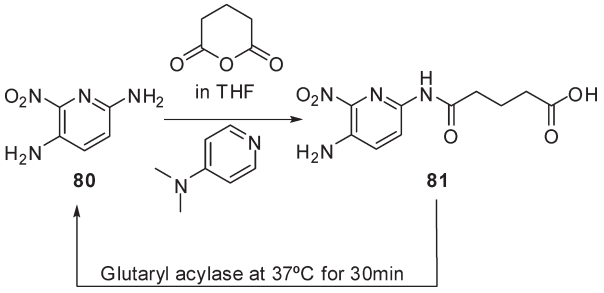


color.[407] Indeed, the study showed that the application to gray or light human hair of a mixture of lead oxide and calcium hydroxide in a small amount of water produces lead sulphide crystals with a size of ~5 nm, with the sulfur being provided by the amino acids of hair keratins involved in the reaction. More recent developments in nanotechnology are providing new possibilities for permanent dye hair applications. Chemically functionalized and physically modified carbon nanotubes are claimed to impart a thin black coating that results in a smooth feel to the hair while also producing a volumizing effect.[408] Of particular interest is the increased surface area of these nanoparticles enhancing contact and interaction with the hair and, as a consequence, producing a longer-lasting black color.

7.3. Reactive Dyeing[409]

Reactive dyes[410−418] applied to textiles form a covalent bond with the substrate, generally between a C-atom of the dye and an O-, N-, or S-atom from hydroxy, amino, or thiol groups on the fibers. Reactive dyes are most important commercially for

Scheme 20. Enzymatic-Labile Dye Precursors Technology



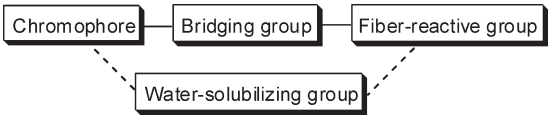
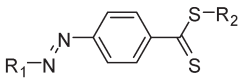


Figure 3. Schematic representation of a reactive dye.

cellulosic fibers, but specific dyes have also been developed for protein (wool and hair[419,420]) and certain synthetic fibers. Their success on textiles is mainly due to superior washfastness and the wide range of brilliant colors available. A reactive dye (Figure 3) comprises four main structural features: the chromophore, which essentially gives the molecule its color and may contribute to features such as lightfastness; a water-solubilizing group, usually the sulfonate group as its sodium salt; the fiber-reactive group, which is capable of chemically reacting with the fiber; and a bridging group, which links the chromophore to the reactive group. The concept of linking dye molecules covalently to hair has also attracted considerable attention. In addition to producing bright colors with excellent washfastness, it is envisaged that an appropriate reactive dyeing method might give improved resistance to fading from the action of perspiration or hair spray and would potentially simplify the dyeing of new hair growth because the previously dyed hair would provide fewer binding sites for new dye m olecules. Another advantage over the oxidative process would be the potential to avoid using hydrogen peroxide and alkali for color development.

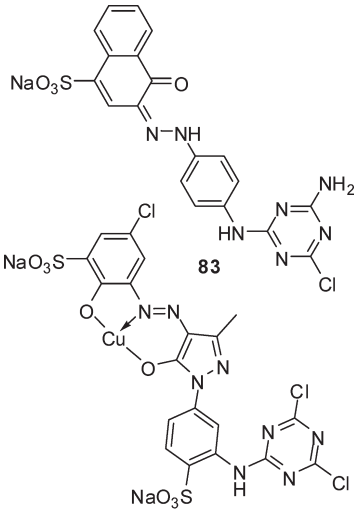
Originally, reactive dyes were believed to be unsuitable for a hair dyeing process because minimal coloration could be achieved with the mild conditions required. An early process for reactive hair coloration was patented in 1968 using halotriazinyl reactive dye.[421] The reactive groups claimed were dichlorotriazinyl, thiosulfate (*Bunte salt*), and β-sulfatoethylsulfone, giving yellow to red colors depending on the chromophore. The dichlorotriazinyl group reacts by heteroaromatic substitution under specific base catalysis, from reaction with a nucleophilic group ($-S^-$) on the hair fiber. The thiosulfate group reacts with free thiol groups, generated from a mordanting pretreatment of the hair fiber, under alkaline conditions to produce disulfide compounds. The β-sulfatoethylsulfone reactive group reacts by nucleophilic addition, preceded by a general base-catalyzed elimination of HSO_4^-. However, the process required pretreatment with a mercaptan, such as thioglycolic acid, thiolactic acid, thioglycerol, or 2,6-dioxythiophenol solution, to generate the S^- ion necessary to covalently bind the dye to the hair fiber at 20 °C, as described in early patents.[5] Using ammonium thioglycolate, dyes containing benzodithioate and substituted carbonothioylthioacetic acid groups reactive toward amines and aminoproteins were patented.[422] It is reported

that hair may be dyed in yellow to blue colors using reactive azo dyes based on thioester **82**.



82
R_2=CH_2COOCH_3 or CH_2CH_2OH

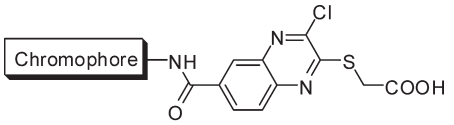
Reactive dyeing of hair using a process inspired by melanin biosynthesis, incorporating a mercaptan pretreatment, has been proposed. Reactive dyes are combined with a melanogenesis activator to dye hair oxidatively using DOPA (**2**), tyrosine, and DHI (**7**). With carefully controlled oxidizing agent proportions, a complete range of brown to black shades is claimed.[423] Nevertheless, this patented process has not been so far exploited commercially.



83

84

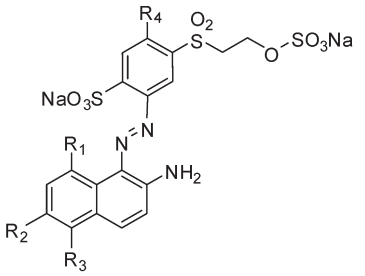
A process eliminating the mercaptan pretreatment has been claimed in which a reactive dye is incorporated into a shampoo solution to dye hair, initially at an acidic pH, adjusted to alkaline after 10 min.[424] The process uses dichlorotriazinyl dyes of metal-free monoazo (**83**) and copper-complexed monoazo (**84**) types, imparting a golden-brown color with good leveling and wetfastness properties. Another mercaptan-free process combines two technologies—an azide photoreactive dye and a condensation reaction between amino and carbonyl compounds, with the process relying on sunlight or UV irradiation for color development, mainly to browns.[425] The details of the reactions occurring within the hair are unclear but probably involve photolytic generation of a highly reactive nitrene from the azide,[426] which reacts with a nucleophilic site within the hair, or an amino group,[427] together with carbonyl group condensations.



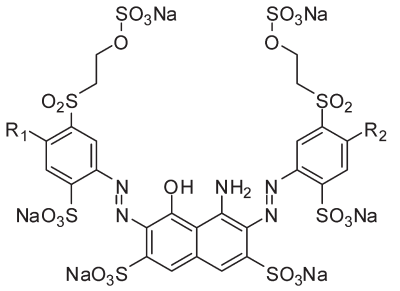
85

Patents have made use of specific reactive dyes for coloring keratinous fibers. The novel fiber-reactive group, the heterofunctional chlorothioglycolato quinoxaline **85**, has been proposed.[428] The chemistry is related to the processes described in the early patents[421,422] by using the thioglycolic acid group as a reducing agent to generate, on the hair fiber, the nucleophilic thiol group necessary to bind the dye. Azo, nitro, and anthraquinone chromophoric groups are claimed.

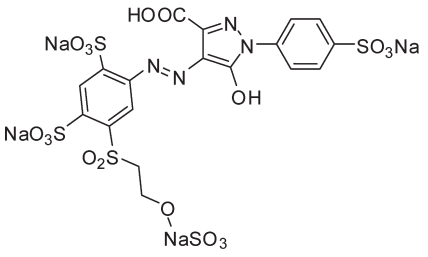
More conventional mono- and bisazo dyes with the β-sulfatoethylsulfone fiber-reactive group have been patented for hair dyeing. A simple aqueous process is claimed involving dyeing hair at 36 °C and pH 7 for 20 min, giving red shades (with **86**−**88**), blue shades (with **89**−**91**), and yellow−brown (with **92**).[429]



86: R_1=R_2=H, R_3=R_4=$NaSO_3$
87: R_1=OH, R_2=R_4=$NaSO_3$, R_3=H
88: R_1=OH, R_2=$NaSO_3$, R_3=R_4=H

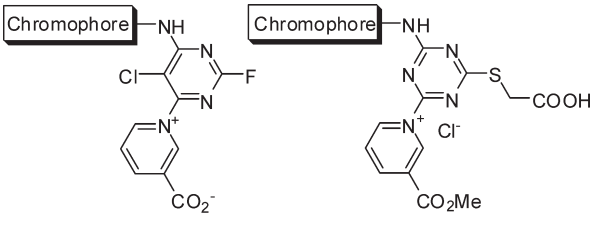


89: R_1=R_2=H
90: R_1=$NaSO_3$, R_2=H
91: R_1=R_2=$NaSO_3$



92

Reactive hair dyes with cationic functionality in the reactive groups have been proposed, for example, quaternary ammonium groups derived from DABCO (1,4-diazabicyclo[2,2,2]octane), *N*-methylmorpholine, and *N*,*N*-dimethylpiperazine.[430] Patents have been issued on reactive dyes, such as **93**[428] or **94**, with an attached pyridinium salt functionality acting as one of the leaving groups.[431]



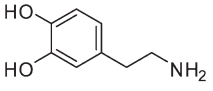
93 **94**

dx.doi.org/10.1021/cr1000145 |*Chem. Rev.* 2011, 111, 2537–2561

Hair coloring products based on reactive dyes do not appear to have reached a commercial outcome. Although they can offer high color strength and outstanding washfastness, they may show only moderate lightfastness. In addition, the requirement to assess their toxicological profile to achieve their approval and registration as hair dyes involves significant cost, the level of which may be prohibitive for their introduction to the market.

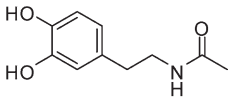
7.4. Technology Based on the Simulation of Natural Hair Pigmentation

The challenge to mimic synthetically (ideally to duplicate) melanin formation inside the hair fiber has understandably attracted attention. Beyond the possibility to produce colors on hair with natural appearance, the ability to designate a product as "natural", and thus presumably nonmutagenic, nontoxic, and nonallergic, would provide a very attractive market possibility. However, the challenge is immense, since natural hair color is determined not only by melanin structure and content but also by the sizes of the particles and their density throughout the hair (section 3). Attempts have been made to imitate the biosynthetic pathway to eumelanin and pheomelanin, by oxidation of identified intermediates. An early patent, introduced soon after the discovery that melanin formation results from enzymatic action on tyrosine, claimed a dye composition comprising an aqueous solution (pH 6−8) of tyrosine (**1**) or DOPA (**2**) and the tyrosinase.[432] A light brown color was obtained, with its intensity depending on tyrosine concentration. Re-dyeing was needed to build up the color. Subsequently improved processes were claimed to produce a wide range of natural shades from light blonds to very dark blackish-brown, using DOPA in combination with derivatives of hydroquinone[433] or diamines and aminophenols,[434] and with the tyrosinase replaced with hydrogen peroxide as the oxidizing agent. In these two patents, "indications" of reactions between the keratin molecule and the dye were proposed but not explained. Problems related to the use of DOPA in this way included its insolubility in water and the limited shades obtained, i.e., black and gray when used alone. Esters of DOPA, soluble in water, and lipid solvents were proposed.[435] These esters resulted in less reactive species and consequently lighter brown colors.[432] It was reported that the addition of a β-alanine derivative significantly enhances oxidation of a tyrosine derivative such as DOPA or dopamine (**95**) to synthetic melanin.[436,437]



95

According to these patents, the lighter colors obtained were believed to be due to varying proportions of a gold-colored complex molecule in the hair matrix. This species was assumed to involve β-alanine complexed with a dihydroxytyrosyl derivative with a side chain not available for indolization. It has been claimed that β-alanine reacts with the quinone resulting from oxidation of DOPA by copper(II) chloride to give a blond hair color. Dopamine (**95**) and its *N*-acetyl derivative (**96**) are reported alternatives to DOPA, giving blond and black colors, respectively.

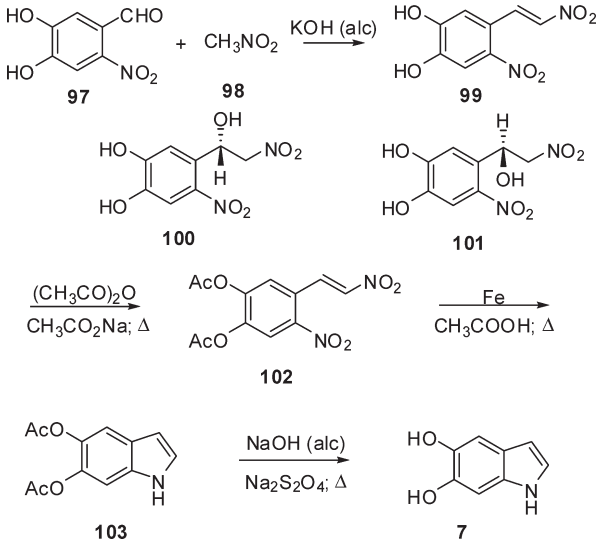


96

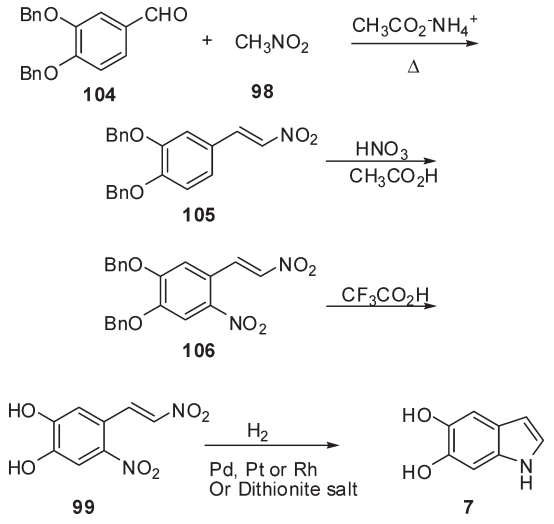
In the last two decades, only two patents have been published on oxidation of DOPA derivatives to mimic melanin biosynthesis. Dopamine (**95**), oxidized with sodium periodate or iodate and a dye dispersion assistant, is claimed to give black and auburn colors depending on the oxidizing agent, with brown shades produced from mixtures with DOPA.[438] Alternatively, DOPA dissolved in hydrochloric acid with potassium ferricyanide as the oxidizing agent, and the pH raised to 6−7 for dyeing, provides black and gray shades on hair,[439] extended to a wider range of colors by mixing with other derivatives.[433−435]

There has been a particular focus on the use of DHI (**7**), the closest isolable intermediate in melanin biosynthesis, which presumably requires less chemistry for conversion. The earliest patent claimed that hair dyeing at acidic pH for 20 min followed by air oxidation generated a gray shade that gradually changed to black.[440] Oxidation with hydrogen peroxide was reported to give gray and light brown colors. To produce stronger colors with shorter exposure times, hair was dyed with DHI using hydrogen peroxide, with iodide as a catalyst, either at acid[441,442] or alkaline pH, achieving mainly chestnut-brown and black shades.[443] The colors could be lightened with a hydrogen peroxide post-treatment to provide gray shades. The use of hydrogen peroxide as a lightening agent could be avoided using a metal ion promoter, such as a cerium salt.[444] Metal salts such as Ce(III), Cu(II), Fe(II), and Mn(II) salts were known to promote melanin formation from DHI. Cerium salts offered more uniform hair coloration and avoided the undesirable glints given by the other metal ions when the dyed hair was subjected to shampooing. It was claimed that Cu(II) salts could be used, but for shades other than black or gray, the use of hydrogen peroxide was required.[445] It was also claimed that hair could be dyed brown using DHI and a metal ion promoter, with a hydrogen peroxide post-treatment. The use of sodium chlorite was claimed not to damage hair, in contrast to hydrogen peroxide, and to color evenly by oxidizing DHI, generating synthetic melanin inside the hair.[446] However, only gray and black shades were obtained. Color formation from DHI lacked "warm" reddish tones if hydrogen peroxide was not used. Moreover, there are several problems associated with its use. It is extremely unstable in air, rapidly decomposing to species ineffective as hair colorants. To enhance its storage stability in aqueous dyeing compositions, the use of water-miscible organic solvents in the composition was claimed.[447] An alternative way to conserve the dyeing capacity of DHI involved packaging the dye composition in a pressurized aerosol device, which also offered the advantage of use in a single-step hair coloration process relying on atmospheric oxidation to develop the color.[448] Careful pH regulation is required to retain the dyeing capacity of DHI.[449,450] It has also been proposed that mixing DOPA or its hydrochloride salt with a hexacyanoferrate(III) oxidant under anaerobic conditions in an aqueous medium gives dopachrome (**5**), which undergoes rearrangement leading in situ to DHI.[451]

Scheme 21. Synthesis of DHI from 4,5-Dihydroxy-2-nitrobenzaldehyde



Scheme 22. Synthesis of DHI from 3,4-Bis(benzyloxy)-benzaldehyde

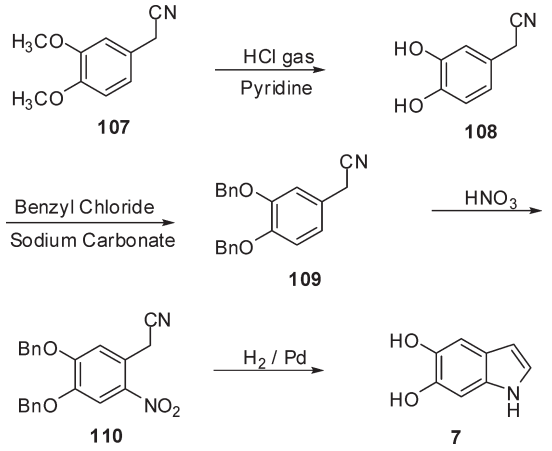


DHI has proved difficult and expensive to synthesize. A synthetic route was devised to give the compound in an overall 35% yield (Scheme 21).[452]

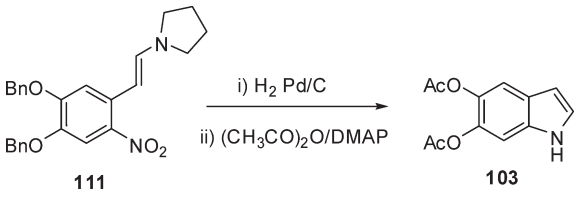
The search for more efficient syntheses have attracted attention not only because DHI is a melanin precursor but also because of interest in the compound as an antioxidant[453] and as an intermediate in the formation of amino acids, alkaloids, and tryptamines.[454] A synthesis from 3,4-bis(benzyloxy)benzaldehyde (**104**) was devised as shown in Scheme 22.

The condensation of **104** with nitromethane (**98**) gives compound **105**, which is then nitrated with fuming nitric acid to produce 1-((2-(benzyloxy)-4-nitro-5-((*E*)-2-nitrovinyl)phenoxy)-methyl)benzene (**106**). Deprotection gives the key intermediate 4-nitro-5-((*E*)-2-nitrovinyl)benzene-1,2-diol (**99**), which is reduced either by hydrogenation in a 50% yield[455] or by dithionite in 40−45% yield[456] to give DHI (**7**). A further improvement involved

Scheme 23. Synthesis of DHI from 2-(3,4-Dimethoxyphenyl)acetonitrile



Scheme 24. Synthesis of 5,6-Diacetoxyindole (DAI)



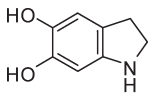
a route via 2-(4,5-bis(benzyloxy)-2-nitrophenyl)acetonitrile (**110**) (Scheme 23). This compound undergoes cyclization by hydrogen transfer at reflux in an isopropanol, hexane, and water mixture, or by hydrogenation with palladium on charcoal. DHI was obtained in an overall 60% yield.[457,458]

Thus, improved yields of DHI have been achieved, but its instability in air and elaborate synthesis remain major hurdles. Attempts have been made to use 5,6-diacetoxyindole (DAI, **103**), an intermediate of the original DHI synthesis as described in Scheme 19, which polymerizes less easily in air due to protection by acetylation. DHI may be obtained through deacetylation of DAI at alkaline pH. A hair coloring composition has utilized a process in which DAI is converted to DHI just prior to application to hair, with thioglycolic acid incorporated both as the mercaptan derivative and as a reducing agent.[459] A wide range of shades was obtained, depending on the composition, from ash blond, reddish chestnut, brown, gray, to black. Methyl derivatives of DHI, such as *N*-methyl-5,6-dihydroxyindole, 5,6-dihydroxy-2-methylindole, and 5,6-dihydroxy-3-methylindole, were claimed to provide similar shades. A one-pot synthesis from 1-(4,5-bis(benzyloxy)-2-nitrostyryl)pyrrolidine (**111**) provides DAI in 65% yield (Scheme 24).[460]

5,6-Dihydroxyindoline (DHIN, **112**) has been used in an attempt to synthesize melanin within the hair.[461,462] This compound was prepared by ether cleavage of 5,6-dimethoxyindoline with aqueous hydrogen bromide.[463] By frequent application of DHIN, gray hair can be restored to natural medium blond to dark brown hair colors, while the combined use of DAI and DHIN produces medium to light brown as well as blond colors. DHICA (**6**), also identified as a melanin biosynthesis intermediate, has been used to dye gray hair brown shades using a copper, zinc, or iron salt at alkaline pH.[464] It is

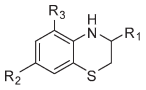
dx.doi.org/10.1021/cr1000145 |*Chem. Rev.* 2011, 111, 2537–2561

unclear as to whether the chemistry involves the formation of DHI, and whether melanin is produced effectively inside the hair.



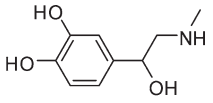
112

Thus, a range of eumelanin precursors have been incorporated in hair coloring compositions, although it is likely that eumelanin formed under the various conditions is dispersed through the fiber, rather than deposited in granules, so that the nuances of the natural process are not imitated. The other hair pigment, pheomelanin, has been the subject of similar research, although the intermediates are more difficult to synthesize. Nevertheless, a process to dye hair using 3,4-dihydro-2H-benzo[*b*][1,4]thiazines (**113**), related to compounds identified as intermediates in pheomelanin formation, has been reported to generate pheomelanin by oxidation inside the fiber.[465] The color achieved using various derivatives at neutral pH with sodium iodate or periodate as oxidizing agents range from blond to brown.



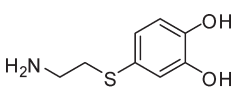
113

A complete naturally based hair coloring process has been reported to perform as well as the commercially used permanent hair dyes.[466] To produce eumelanin inside the hair fiber, DOPA and its methyl esters derivatives have been used, as previously described,[435] and by introducing sulfur-containing nucleophiles, red and yellow pheomelanins were produced, thus broadening the range of colors achievable using such a process. Adrenaline (**114**), which is less susceptible to polymerization, was also used, for example, giving brown shades when used with DOPA methyl esters with an oxidant. The introduction of common hair dye components, including compounds **22** and **25**, *m*-aminophenols, and resorcinol, gave reactions with dopaquinone (**3**) leading to brown shades. This process had been previously discussed in patents.[433,434]



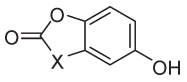
114

Reports of attempts to produce pheomelanin inside the hair using hydroxybenzothiazines noted significant differences in color by incorporating certain nucleophiles, such as 4-(aminoethanethio)catechol (**115**) and cysteine, into the compositions with careful control of dyeing conditions.[465]



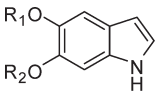
115

In addition to the processes using identified melanin precursors, derivatives of the natural intermediates have been described to generate color on hair by oxidation. For example, oxidative dyeing using 5-hydroxy-3*H*-benzofuran-2-one (**116**) or 5-hydroxybenzo[1,3]dioxol-2-one (**117**) is claimed to give brown shades, whereas a mixture of 5-hydroxybenz[1,3]oxazole-2-one (**118**) and 5-hydroxybenz[1,3]oxathiol-2-one (**119**) provides golden blond colors.[467]

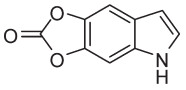


116: X = CH_2
117: X = O
118: X = NH
119: X = S

New indole derivatives have been patented to address the issue that DHI only achieves black and gray shades. A series of indole compounds were synthesized[468] using the penultimate step in the synthesis shown in Scheme 21,[452] with the appropriate starting materials **120**−**123**. Mainly blond shades were obtained when the hair was dyed in a process whereby gray hair was treated with aqueous monoethanolamine and copper(II) sulfate, followed after 5 min by treating with the indole derivative in aqueous ethanol at alkaline pH.



120: R_1=CH_3, R_2=H
121: R_1=R_2=$Si(CH_3)_3$
122: R_1=H, R_2=CH_3



123

Monohydroxyindoles have been claimed as dye precursors with sodium periodate in a system reported to allow the dye to penetrate more easily into the hair without coating the hair shaft, thus giving a more pleasing and stable dyeing.[469]

8. CONCLUSIONS AND FUTURE PROSPECTS

These past few decades have witnessed a significant growth in our understanding of the chemical and physical properties of hair structure, of the mechanisms involved in the hair dyeing process, and of the inter-relationships between these two features. The enhanced knowledge of the composition of the hair fiber, in particular the chemical structure of its outer boundary, and an emerging understanding of dye diffusion pathways and the factors influencing the process kinetics are assisting the development of tailored dye precursors and of new technologies that are commonly aimed at achieving more intense and durable permanent hair coloration. In addition, numerous studies have generally served to address the perennial concerns on toxicological issues associated with the most important commercial permanent hair dyeing technology based on the oxidative process derived from Hofmann's discovery about 150 years ago. The considerable number of new dye precursors patented over the years, the pace of which does not appear to be slowing, and examples of recent commercial success such as the diamino-*N*,*N*-dihydrazopyrazolones, suggest that the oxidative process in an optimized form will remain the dominant technology into the foreseeable future. The expense associated with the approval process for new formulation ingredients, enforced by social pressures and legislation, is certain to limit the introduction of new dye precursors to those for which there is unequivocal evidence for a commercial investment return. Nevertheless, there remains considerable scope for research toward new technologies for permanent hair coloration, conceivably through intensified investigation of some of the alternative technologies identified in this review. The rapidly developing science of genetics and an emerging understanding of the molecular basis of hair pigmentation

may be key elements in the development of systems encouraging natural, biotechnological, or semisynthetic hair repigmentation. Although there has been some preliminary success in this area delivering coloring agents to hair follicles,[470−472] further development is essential before the technology is ready for the consumer. A growing understanding of the principles of greying of hair, and the possibility of its inhibition or prevention, may well accelerate this development.[473] The explosive growth in nanotechnologies is certain to continue to attract the interest of hair color chemists, for example, to exploit the potential of photonics to make use of materials that manipulate light to create bright colors without using traditional coloring materials, as one way of addressing potential environmental and toxicological concerns.

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Olivier Morel received his Masters degree in Chemistry in 2002 at the Ecole Nationale Superieure de Chimie de Lille, France. Within Robert Christie's research group at Heriot-Watt University, he was awarded a Ph.D. in 2006, based on the thesis "Molecular modelling and synthetic studies in novel approaches to hair coloration". He has presented several conference papers, in particular at the 22nd IFSCC Congress in 2002 and the Hair Color Global Forum in 2005. Currently, he is the R&D Manager at Xennia Technology Ltd. His major research interests are in exploring new coloration technologies applicable to various substrates through the development of new processes and developing novel high-tech colorants.

Robert Christie is Professor in Colour Chemistry & Technology in the School of Textiles & Design of Heriot-Watt University, Scotland, U.K. His career has also included periods in industry with Ciba and Dominion Colour Corporation. His research interests are in organic pigments—molecular and crystal design in relation to application performance, fluorescent dyes, hair dyes, chromic textiles, and inkjet printing. He also collaborates with textile designers at the technology interface. He has published 5 textbooks and more than 90 journal articles and patents. He was given the 2008 Worshipful Company of Dyers of London award for research excellence in color science.

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