Diazo Coupling Reactions with a Functional Micellar Reagent. Circumvention of Hartley's Rules

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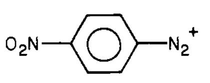
Abstract: The surfactant *N*-*n*-cetyl-*N*,*N*-dimethyl-*N*-*p*-aminobenzylammonium bromide and the corresponding *N*,*N*,*N*-trimethyl-*N*-*p*-aminobenzylammonium bromide model compound were synthesized and diazotized with nitrous acid. Each resulting diazonium ion was coupled to 2-naphthol and to 2-naphthol 6-sulfonate ion. Rate constants for all of the coupling reactions were determined under various conditions of pH. Azo coupling with the micellar diazonium ion surfactant was faster than azo coupling with the model diazonium ion by factors of 122 (2-naphthol) and 244 (2-naphthol-6-sulfonate) at pH 7.1. Mechanistic aspects of these reactions are discussed, and it is demonstrated that they are catalyzed by cationic micelles even though they involve cationic intermediates.

Introduction

Hartley[1] formulated a "sign rule" to explain shifts of indicator equilibria in the presence of simple cationic or anionic surfactant micelles.[2] A corollary applies to kinetic systems: "Reactions involving anions are catalyzed by cationic micelles and inhibited by anionic ones... Reactions involving cations are catalyzed by anionic micelles and inhibited by cationic ones..."[3]

These ideas are well illustrated by the attempted micellar catalysis of diazo coupling between *p*-nitrobenzenediazonium (**1**) and 2-naphthol-6-sulfonate (**2a**) ions.[4] The rate constants for coupling were depressed, relative to the rate constants in water, in both cationic micellar cetyltrimethylammonium bromide (CTABr) and anionic micellar sodium lauryl sulfate (NaLS) solutions (factors of 3.1 and 8.1, respectively, in 0.01 M surfactants).[4] Application of the simple electrostatic arguments[1-3] suggests that, although micellar CTABr will solubilize anionic substrate **2a**, it will exclude cationic reagent **1**, whereas micellar NaLS will solubilize **1**, but exclude **2a**; accordingly, coupling reactions should be inhibited in each case.



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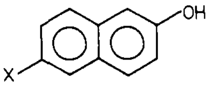
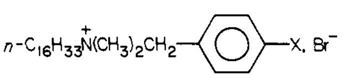


2(a, X = SO_3^-; b, X = H)

This electrostatic impasse could be circumvented if a cationic surfactant were *functionalized* with an aryldiazonium ion moiety; anionic substrates would still be readily solubilized, but the diazonium ion could not be "excluded" and catalysis should be realized. We now report the successful reduction of this idea to practice.

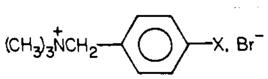
Results and Discussion

Anilino-functionalized surfactant **3a** and model compound **4a** were synthesized. *p*-Acetamidobenzyl alcohol was converted to the analogous bromide,[5] which was quaternized with either *N*,*N*-dimethylcetylamine[6] to give *N*-acetyl-**3a** or with trimethylamine to give *N*-acetyl-**4a**. These precursors were characterized by NMR spectroscopy and elemental analysis. Cleavage of the acetyl moieties (10% HBr in aqueous CH_3OH, 60 °C, 48 h), followed by neutralization, lyophilization, and crystallization from ethereal methanol, gave surfactant **3a** and model **4a**. The critical micelle concentration (cmc) of **3a**·HBr was 5.3×10^{-5} M (surface tension 20 °C, pH 2.5, μ = 0.1, KCl), whereas no surface activity was observed for **4a**·HBr, under comparable conditions, over the concentration range 5×10^{-4} to 5×10^{-2} M.



$n\text{-}C_{16}H_{33}\overset{+}{N}(CH_3)_2CH_2\text{-}C_6H_4\text{-}X,\ Br^-$

3(a, X = NH_2; b, X = N_2^+, Br$^-$)



$(CH_3)_3\overset{+}{N}CH_2\text{-}C_6H_4\text{-}X,\ Br^-$

4(a, X = NH_2; b, X = N_2^+, Br$^-$)

Table I. Pseudo-First-Order Rate Constants for Coupling of 3b to β-Naphthol, pH 7.1, 4 °C, μ = 0.1 (KCl)[a]

10^3[3b], M[b]	k_ψ, s^{-1} [c]	10^3[3b], M[b]	k_ψ, s^{-1} [c]
2.5	26.4	0.0050	0.0848
1.5	23.8 ± 0.2_2	0.0010	0.0137
0.83	20.3 ± 0.7_3	0.000 25	0.0092
0.24[d]	3.1 ± 0.1_2		

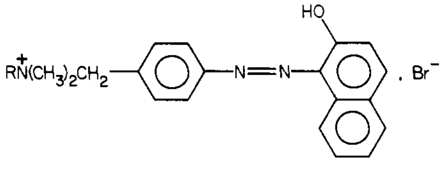
[a] Followed at 485 nm. [b] Final concentrations. Solutions containing twice these concentrations of 3b were prepared in 0.05 M phosphate buffer, pH 6.55, and reacted in the stopped-flow spectrometer with solutions of β-naphthol in 0.05 M phosphate at pH 8.1. The final pH was 7.1 ± 0.05. Final [β-naphthol] were 5×10^{-6} (first three runs) or 8×10^{-7} M (last three runs). [c] Errors are average deviations of *n* reactions. [d] This reaction gave identical results at either substrate concentration.

Table II. Pseudo-First-Order Rate Constants for Coupling of 3b and 4b to β-Naphthol, 4 °C[a]

diazonium ion	final pH	k_ψ, s^{-1} [b]	$k_\psi{}^{3b}/k_\psi{}^{4b}$ [c]
3b	5.95	5.9 ± 0.1_4	164
4b	5.95	0.084 ± 0.01_3	
3b	7.10	23.8 ± 0.2_2	98
4b	7.05	0.57 ± 0.02_4	
3b	7.85	216 ± 4_2	26
4b	7.75	19.2 ± 0.9_4	

[a] Final concentrations: [3b] = 1.5×10^{-3} M, [4b] = 3.5×10^{-3} M, [2b] = 5×10^{-6} M, 0.05 M phosphate, μ = 0.1 (KCl). Reactions were followed at 485 nm. [b] Errors are average deviations of *n* experiments. [c] These values are corrected for the differing concentrations of 3b and 4b (rate-constant ratios have been multiplied by 3.5/1.5 = 2.3).

Anilines **3a** and **4a** were diazotized ($NaNO_2$, 48% aqueous HBr, pH 2, 5 °C, 15 min) and the resulting diazonium ions **3b** and **4b** were neutralized and coupled to β-naphthol (**2b**) at pH 7, affording the red azo compounds **5** and **6**, which were characterized.[7]



5, R = n-$C_{16}H_{33}$; 6, R = CH_3

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(1) Hartley, G. S. *Trans. Faraday Soc.* **1934**, *30*, 444.
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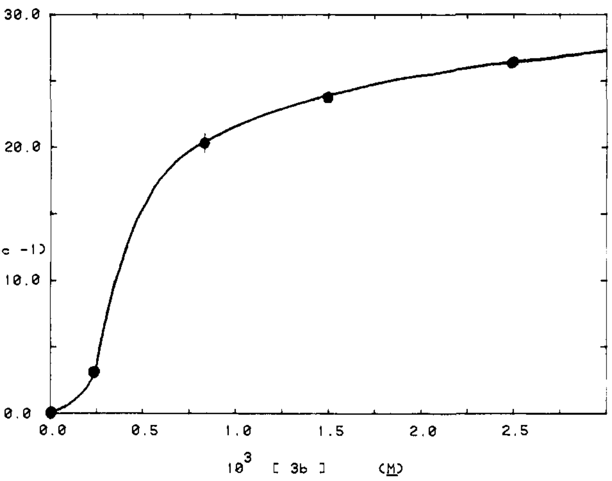

Figure 1. Pseudo-first-order rate constants for coupling of surfactant diazonium ion **3b** to β-naphthol, pH 7.1, 4 °C, μ = 0.1 (KCl). k_ψ^{max} was obtained at the solubility limit of **3b**. For convenience of display, only the first five entries of Table I are depicted in the Figure; the first four entries represent micellar reactions ([**3b**] > cmc ~ 5 × 10^{-5} M), whereas the fifth entry corresponds to a submicellar reaction. A Lineweaver–Burk analysis[2] of the micellar data points gives k_m ~ 30 s^{-1}; k_ψ^{max}(obsd) = 26.4 s^{-1}. See text and Table I.

Kinetics of these coupling reactions were investigated by stopped-flow spectroscopy under various conditions;[8] with the diazonium ions in excess, good pseudo-first-order (r > 0.999) kinetics were observed. A rate constant vs. [surfactant] profile for the coupling of **3b** to **2b** is summarized in Table I and displayed in Figure 1.

The typical concentration dependence expected for a micelle-catalyzed reaction[2] is clearly seen. The maximum observed rate constant, k_ψ = 26.4 s^{-1}, was obtained at the solubility limit of **3b**.

The extent of micellar catalysis can be judged from the data in Table II, in which coupling reactions of micellar **3b** and nonmicellar **4b** are compared at pH 6–8. The micellar reactions are significantly faster in each case, the extent of catalysis ranging from 26 at pH 7.8 to ~160 at pH 6. The magnitude of catalysis is superficially consistent with binding of **2b** by micellar **3b**, with attendant conversion of a bimolecular to a pseudounimolecular reaction.[9] However, the *apparent* overall catalysis is undoubtedly a summation of micellar perturbation of several independent factors. For example, the transition state for azo coupling, whether it involves formation or destruction of an intermediate σ complex, will be less charge localized than the ground state, and will be stabilized in a less polar (micellar) environment.[10]

Additionally, both **3b** and **4b** couple more rapidly with **2b** as the pH is increased. This is due to increasing participation of β-naphthoxide ion, the active form of the substrate.[10] β-Naphthol, solubilized in a cationic micelle, will be more extensively ionized[11] to anionic β-naphthoxide at any external pH, so that a factor of ~4.5[11] of the rate advantage in coupling with micellar **3b** can be attributed to this micellar "acid strengthening" effect. One notes, however, that, although the absolute rate constants for coupling increase with pH, the relative rate constant, k_ψ^{3b}/k_ψ^{4b}, *decreases* with increasing pH. We tentatively ascribe this to increasing conversion of micellar diazonium ion **3b** to the unreactive diazotate form (ArN=NO$^-$).[10a] At any pH, this conversion to an anion via reaction with OH$^-$ should be more extensive for cationic micellar **3b** than for nonmicellar **4b**, and would partially offset the rate-enhancing effect of augmented β-naphthol ionization.

Table III. Pseudo-First-Order Rate Constants for Coupling of 3b and 4b to **2a** and 2b, pH 7.1, 4 °C[a]

ArN_2^+	concn, ×10^3 M	substrate	k_ψ, s^{-1} [b]	k_ψ^{3b}/k_ψ^{4b} [c]
3b	1.5	2b	24.8 ± 0.8_2	122
4b	2.5	2b	0.34 ± 0.02_3	
3b	1.5	**2a**	22.2 ± 0.4_3	244
4b	2.5	**2a**	0.152 ± 0.002_3	

[a] Conditions = 0.03 M phosphate buffer, μ = 0.1; [2b] = 8 × 10^{-7} M; [2a] = 1.25 × 10^{-5} M. Reactions with 2b and **2a** were followed at 485 and 495 nm, respectively. [b] Errors are average deviations of n experiments. [c] These values are corrected for the differing concentrations of 3b and 4b (rate-constant ratios were multiplied by 2.5/1.5 = 1.67).

Finally, the coupling reactions were extended to 2-naphthol-3-sulfonate (**2a**). Kinetic results appear in Table III, where they are compared with analogous data for 2-naphthol (**2b**). Micellar catalysis is evident in both cases and is somewhat *stronger* with substrate **2a**, presumably owing to more favorable electrostatic factors. That is, at low concentrations, the "permanent" anion, **2a**, is more favorably bound to the cationic micelles than is the largely neutral (at pH 7.1)[11] **2b**. Under the conditions of Table III, this advantage is translated into a differential micellar catalytic advantage of ~2 for surfactant diazonium ion **3b** coupling to substrate **2a**, as opposed to substrate **2b**, relative to the corresponding nonmicellar coupling reactions of diazonium ion **4b** in each case.

It is now clear that micellar catalysis can be observed in *electrophilic* aromatic substitution reactions.[12] More importantly, the use of functional micellar reagents permits such catalysis to occur in *cationic* micelles, enabling the effective circumvention of Hartley's rules, as in the diazo coupling of **3b** to **2a**.

Experimental Section[13]

***N-n*-Cetyl-*N,N*-dimethyl-*N-p*-acetamidobenzylammonium Bromide (3, X = NHAc).** Unrecrystallized *p*-acetamidobenzyl bromide[5] (2 g, 8.8 mmol) and 4 g (15 mmol) of *N,N*-dimethylcetylamine[6] were added to 50 mL of nitromethane. The mixture was stirred for 3 h at 25 °C, after which time the precipitate was collected on a Büchner funnel and washed with a little nitromethane. After two recrystallizations from EtOAc (Norite was used in the first recrystallization), we obtained 3 g (6.0 mmol, 68%) of the title compound as white prisms, mp 152–153 °C. NMR (δ, $CDCl_3$): 0.90 (t, 3 H, $CH_3(CH_2)_{14}$), 1.30 (s, 28 H, $(CH_2)_{14}$), 2.33 (s, 3 H, CH_3CO), 3.67–3.17 (m + s, 8 H, Me_2N^+-$CH_2(CH_2)_{14}$), 4.97 (s, 2 H, N^+CH_2Ar), 8.0–4.47 (A_2B_2 q, 4 H, aryl).

Anal. ($C_{27}H_{49}N_2OBr$) C, H, Br.

***N,N,N*-Trimethyl-*N-p*-acetamidobenzylammonium Bromide (4, X = NHAc).** Unrecrystallized *p*-acetamidobenzyl bromide[5] (1.7 g, 7.5 mmol) and excess condensed trimethylamine were added to 25 mL of nitromethane in a screw-top Carius tube at -20 °C. The tube was sealed and allowed to stand, with occasional shaking, at 25 °C for 3 h. After the tube was cooled and opened, excess trimethylamine was allowed to escape, and the contents were filtered on a Büchner funnel. The precipitate was washed with cold absolute ethanol and then recrystallized from this solvent to afford 1.4 g (4.9 mmol, 65%) of the title compound as fine, slightly yellow needles, mp 252 °C. NMR (δ, D_2O, DSS): 2.27 (s, 3 H, CH_3CO), 3.20 (s, 9 H, Me_3N^+), 4.77 (s, 2 H, CH_2N^+), 7.57 (s, 4 H, aryl).

Anal. ($C_{12}H_{19}N_2OBr$) C, H, Br.

***N,N,N*-Trimethyl-*N-p*-aminobenzylammonium Bromide (4a).** Acetamido compound 4 (X = NHAc) was deprotected by dissolving 1.5 g (5.2 mmol) in 4 mL of 48% aqueous HBr and 16 mL of methanol. The resulting solution was heated under N_2 to 60 °C for 48 h and then cooled in an ice bath and diluted with saturated NaOH solution until the mix-

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(7) See the Experimental Section.

(8) Solutions of **3b** and **4b** slowly decomposed at 25 °C; all kinetic studies were therefore carried out at 4 °C, on freshly prepared solutions.

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(11) The pK_a of β-naphthol was spectrophotometrically determined to be 8.86 in 0.05 M CTABr (μ = 0.11, KCl, 20 °C), whereas it is 9.51 in the absence of CTABr (Weast, R. C. "Handbook of Chemistry and Physics,", 57th ed.; CRC Press: Cleveland, 1976; p D-151).

(12) Micellar catalysis has been extensively studied in nucleophilic aromatic substitution reactions (cf. ref 2) but has been largely unexplored in electrophilic cases.

(13) Melting points are uncorrected. UV spectra were recorded on a Cary Model 17D spectrometer. NMR spectra were determined on a Varian T-60 instrument. Chemical shifts are relative to Me_4Si, unless otherwise noted. Microanalyses were done by Robertson Laboratory, Florham Park, N.J.

ture was basic. Solvents were removed under reduced pressure at 60 °C; the residue was dissolved in 10 mL of methanol and dry ether was added until turbidity was evident. Chilling in the refrigerator (18 h) afforded 1 g (4.1 mmol, 79%) of **4a** as white needles, mp 154 °C. NMR (δ, D_2O, DSS): 3.10 (s, 9 H Me_3N^+), 4.40 (s, 2 H, N^+CH_2), 7.53–6.90 (A_2B_2 q, 4 H, aryl). The free amine is unstable to storage and was used immediately upon preparation.

***N*-*n*-Cetyl-*N*,*N*-dimethyl-*N*-*p*-aminobenzylammonium Bromide (3a).** In precisely the same way, acetamido surfactant **3** (X = NHAc) was converted to free base **3a**, mp 185 °C, in 60% yield. NMR (δ, Me_2SO-d_6): 0.85 (t, 3 H, $C\mathit{H}_3(CH_2)_{14}$), 1.27 (s, 28 H, $(CH_2)_{14}$), 3.27–2.90 (m + s, 8 H, $\mathit{Me}_2N^+C\mathit{H}_2(CH_2)_{14}$), 4.33 (s, 2 H, $N^+C\mathit{H}_2Ar$), 7.23–6.57 (A_2B_2 q, 4 H, aryl). The free amine is unstable to storage and was used immediately upon preparation.

Diazotization and Coupling of 3a and 4a. In 30 mL of distilled water were dissolved 0.3 g (1.2 mmol) of **4a** or 0.5 g (1.1 mmol) of **3a**. The solutions were cooled in ice and diluted with solutions of 0.080 g (1.2 mmol) of $NaNO_2$ in 10 mL of water. The pH was reduced to 2 by addition of 48% aqueous HBr, and the solutions were stirred at $t \leq 5$ °C for 15 min. The solutions were then neutralized (ice bath) with 1 N NaOH to pH 7, thus affording solutions of diazonium ions **3b** or **4b**. These solutions are only moderately stable, so that coupling was carried out at once.

To the solution of **3b** or **4b** was slowly added a solution of 0.15 g (1.0 mmol) of β-naphthol in 12 mL of water at pH 10.5. The reaction mixture was stirred magnetically and kept at pH 7 by the addition of small quantities of aqueous HBr as needed. A red precipitate (**5** or **6**) was formed from solutions of either **3b** or **4b**, respectively. These precipitates were filtered and recrystallized.

From **3b**, we obtained, after recrystallization from ethereal ethanol, 0.4 g (0.66 mmol, 60%) of surfactant azo compound **5** as a red powder: mp 183–184 °C; λ_{max} 485 nm, log ϵ ~3.8 (10^{-2} M aqueous CTABr, PO_4 buffer, pH 7, $\mu = 0.1$); NMR (δ, $CDCl_3$) 0.96 (t, 3 H, CH_3), 1.26 (s, 28 H, $(CH_2)_{14}$), 3.83–3.36 (m + s, 8 H, CH_2N^+ and $N^+(CH_3)_2$), 5.37 (s, 2 H, benzyl), 8.46–7.40 (m's, 10 H, aromatic).

Anal. Calcd for $C_{35}H_{52}N_3OBr$: C, 68.88; H, 8.59; N, 6.88. Found: C, 67.6; H, 8.40; N, 6.60.[14]

From **4b**, we obtained, after recrystallization from absolute ethanol, 0.3 g (0.75 mmol, 62%) of azo compound **6** as red needles: mp 221-222 °C; λ_{max} 485 nm, log ϵ ~3.8 (aqueous PO_4 buffer, pH 7, $\mu = 0.1$); NMR (δ, Me_2SO-d_6) 3.20 (s, 9 H, Me_3N^+), 4.77 (s, 2 H, benzyl), 8.80–7.50 (m's, 10 H, aromatic).

Anal. Calcd for $C_{20}H_{22}N_3OBr$: C, 60.0; H, 5.54; N, 10.5. Found: C, 59.1; H, 5.80; N, 10.1.[14]

Kinetic Studies. Solutions of diazonium ions **3b** (0.178 mmol) or **4b** (0.747 mmol) were prepared in 10 mL of water by diazotization of **3a** or **4a**, as described above. Calculated amounts of NaH_2PO_4 or KCl were added for proper ionic strength, and the desired pH was achieved by addition of aqueous HBr or NaOH. The diazonium ion solutions were then diluted to 25 mL with water.[8] Concurrently, 8.5 mg of β-naphthol was dissolved in a total of 500 mL of aqueous solution by addition of 1 M NaOH·NaH_2PO_4 solution. The ionic strength was adjusted to 0.1 with NaH_2PO_4 or KCl; the pH was adjusted as necessary.

Appropriately diluted and pH-adjusted stock solutions of diazonium ion **3b** or **4b** and β-naphthol were charged into the drive syringes of a Durrum Model D-130 stopped-flow spectrophotometer equipped with a Beckman DU-2 monochromator and a Tektronix Model 5103N/D-15 storage oscilloscope. After stopped-flow reactions, the oscilloscope traces were photographed with a Polaroid camera. Constant-temperature circulating baths maintained reaction temperatures at 4 ± 1 °C. All solutions were prepared from nitrogen-purged, steam-distilled water.

Rate constants were obtained from computer-generated linear correlations of log ($A^\infty - A^t$) with time in the standard manner. Reaction traces were generally read to >70% of completion, using at least seven points from the oscilloscope trace. Infinity values were systematically varied to obtain the best least-squares fit. Correlation coefficients were routinely >0.999, and the optimized A^∞ varied by <8% from the experimental value.

Data appear in Tables I–III. Concentrations of all reagents and buffers, ionic strengths, and pHs are detailed in the footnotes of the individual tables. Also included are the appropriate λ values for the kinetics experiments. Tables I and II pertain to coupling experiments with β-naphthol (**2b**); analogous experiments with 2-naphthol-6-sulfonate (**2a**) are summarized in Table III, and were carried out in a completely parallel way.

Acknowledgments. We thank the National Cancer Institute (Research Grant CA-14912) and the National Science Foundation for financial support. The stopped-flow spectrophotometer was purchased under Public Health Service Grant RR-7058-09 to Rutgers University. R.A.M. thanks the Department of Organic Chemistry of the Weizmann Institute of Science for its hospitality during the composition of this manuscript.

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[14] The observed % C was low, due most likely to traces of water absorbed by the hygroscopic salt during the analytical procedures.

Polyanthraquinocyclopropanes, Dianthraquinocyclopropanone, and Dianthraquinoethylene. Synthesis and Properties

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Abstract: Tris(9-anthron-10-ylidene)cyclopropane (**7c**) was prepared by the Friedel–Crafts reaction of 9-methoxyanthracene with trichloropropenium tetrachloroaluminate, followed by demethylation and oxidation of the resulting bis(9-hydroxy-10-anthryl)cyclopropenylidenanthrone. The corresponding triquinocyclopropanes with one or two anthraquino groups replaced by 4-oxo-3,5-di-*tert*-butyl-2,5-cyclohexadien-1-ylidene groups (**7a,b**) were prepared by stepwise addition of 9-methoxyanthracene and 2,6-di-*tert*-butylphenol. Reaction of 2 equiv of 9-methoxyanthracene in an analogous fashion resulted in 2,3-bis(9-anthron-10-ylidene)cyclopropanone (**8**), which loses carbon monoxide photolytically to form dianthraquinoethylene (**9**). These materials are intensely colored, highly conjugated solids with electronic absorptions in the near infrared. Spectroscopic properties and results of Huckel MO calculations are reported.

Recent work in these laboratories has been directed toward the synthesis and characterization of polyquinocycloalkanes. These compounds may be viewed as the fully oxidized analogues of cyclic oxocarbon anions, $C_nO_n^{2-}$,[2] in which one or more of the oxygens have been replaced by a 4-oxo-3,5-dialkyl-2,5-cyclohexadiene moiety (the 3,5-dialkyl substituents are necessary for protection

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[1] (a) Chemical Resources, 3M Co., St. Paul, Minn. 55101; (b) University of Wisconsin.

[2] (a) R. West and J. Niu, "Non-Benzenoid Aromatics", Vol. 1, J. P. Snyder, Ed., Academic Press, New York, 1969, Chapter 6; (b) "The Chemistry of the Carbonyl Group", Vol. 2, J. Zabicky, Ed., Interscience, New York, 1970, Chapter 4; (c) R. West, D. Eggerding, J. Perkins, D. Handy, and E. C. Tuazon, *J. Am. Chem. Soc.*, **101**, 1710 (1979), and references cited therein.

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