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Aryl Carbamates: Mechanisms of Orthosodiations and Snieckus-Fries Rearrangements

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Abstract

Aryl carbamates are orthometalated by sodium diisopropylamide (NaDA) in THF. The resulting arylsodiums undergo Snieckus-Fries rearrangement to give orthoacylated phenols in good yield. The intermediate arylsodiums and resulting ortho-acylated phenolates are suggested to be monomeric. The rate-limiting step in the two-step sequence depends on the steric demands of the carbamoyl moiety and the substituents in the meta position of the arene. Rate studies reveal a dominant disolvated monomer-based orthometalation followed by a di- or trisolvated arylsodium monomer-based rearrangement. Kinetic evidence of a NaDA-catalyzed Snieckus-Fries rearrangement suggests the intermediacy of mixed trimers. Competitive halide eliminations to form benzyne are also discussed.

Graphical Abstract

Introduction

We have an emergent interest in the chemistry of sodium diisopropylamide (NaDA) and the structures and reactivities of the resulting organosodium salts.^{1,2} To say that NaDA has received little interest is an understatement. While lithium diisopropylamide (LDA) is used daily less than two dozen reports of NaDA-mediated metalations appeared over the half century following the first report in 1959.³

NaDA is a much more reactive base than LDA and displays complementary selectivities,^{1a} but its adoption has been constrained by its insolubility in hydrocarbons and its propensity toward decomposition in ethers,^{1b,3} both exacerbating problems with stock solutions. However, trialkylamines⁴ such as *N,N*-dimethylethylamine (DMEA) or *N*-methylpyrrolidine

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Supporting Information: Spectroscopic, kinetic, and computational data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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have been found to afford stable 1.0 M NaDA solutions that can be prepared in minutes from technical-grade reagents on the benchtop without the need for vacuum lines or gloveboxes.^{1a,5} We have characterized NaDA in standard donor solvents^{1b} and studied the mechanisms of its reactions with alkenes, dienes, arenes, and alkyl halides.^{1c-f}

In this paper we describe NaDA-mediated Snieckus-Fries rearrangements (Scheme 1).⁶ The NaDA-mediated metalation step is fast when compared with LDA,⁷ and the subsequent rearrangements afford high yields of ortho-acylated phenols. Arylsodiums bearing halogen substituents may either rearrange or form benzyne, depending on the nature of the halogen and carbamate substituents.⁸

Results and Discussion

NaDA of adequate purity for synthetic applications can be prepared in situ from technical grade diisopropylamine and DMEA in minutes. For the structural and rate studies described herein, however, we take the added precaution of using NaDA recrystallized from DMEA-hexane.^{1a} NaDA in DMEA or hexane containing ≥ 3 equiv of THF forms exclusively the tetrasolvated dimer **5**;^{1b,9} THF/DMEA and THF/hexane may be used interchangeably for generic metalations.^{1c-f}

Substantial spectroscopic, kinetic, and computational data are archived in the Supporting Information. Allusion to results that are unaccompanied by specific data are fully documented therein. Density functional theory (DFT) calculations were carried out at the B3LYP/6-31G(d) level¹⁰ with energies from single-point calculations at the M06-2X level of theory.¹¹ The phrase “computationally viable” alludes to computations affording valid minima and saddle points with a single negative frequency. To homogenize the results, all computations were carried out on the meta fluoro derivatives (the ‘e’ series).

Profile of the Reaction Coordinate.

Aryl carbamate metalations and subsequent rearrangements were monitored using in situ IR spectroscopy¹² by following the absorbances of the starting carbamates **1a–1g** (1720–1734 cm^{-1}), arylsodiums **2b–2g** (1680–1697 cm^{-1}), and sodium phenolates **3a–3g** (1615–1624 cm^{-1}). (See Figure 1.) By adjusting the aryl substituents (X), carbamate *N*-alkyl groups (R), reaction temperature, and substrate deuteration, we were able to independently monitor the metalation and rearrangement steps (Scheme 2). For example, rate-limiting metalation of **1a** is followed by rapid rearrangement to **3a**, which precludes observation of arylsodium **2a**. Switching to the diethylamido moiety (**1b**) has little effect on the rate of metalation, but markedly slows the rearrangement step, causing **2b** to accumulate in a fully established soft (balanced) equilibrium prior to rearrangement. Incorporation of acidifying substituents in the

meta position promotes and accelerates the metalations while decelerating the subsequent rearrangements; arylsodiums **2d–g** form quantitatively prior to rearrangement.

Arylsodium Structures.

Unlike aryllithiums, in which ^6Li - ^{13}C coupling provides intimate structural details,¹³ less direct methods are needed to characterize the arylsodiums. We favor the method of continuous variations (MCV),¹⁴ in which binary mixtures of arylsodiums are monitored by ^1H or $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy (eq 1). In principle, the number and symmetries of heteroaggregates should reveal the aggregation state. In practice, no heteroaggregates were observed. While absence of evidence is not *necessarily* evidence of absence of aggregation, it does appear that the ArNa or ArLi stability required for observable metalation with alkali metal amides is also the precondition that precludes aggregation.^{13b}

DFT computations on **2e** reveal exothermic serial solvation to afford di, tri, and tetrasolvated monomers **6**, **7**, and **8**, respectively (Scheme 3). IR spectroscopy shows a near 50 cm^{-1} shift of the carbonyl to lower energy, suggesting that chelation remains intact. This observation would argue against tetrasolvated **8**, which lacks chelation.¹⁵ Dimerization to generate **9**, which is suggested to form at low THF concentration, is calculated to be endothermic by 8.1 kcal/mol (although such non-isodesmic¹⁶ comparisons should be viewed with great caution).

Substrates **1b** and **1c**, in which arene and arylsodium coexist at equilibrium, appeared to offer an easy experimental probe of arylsodium solvation benchmarked to tetrasolvated NaDA dimer **5^{1b}**, but the results proved confusing. The proportions of ArNa and ArH versus THF concentration (Figure 2) suggest that ArNa monomer **2b** has a *lower* per-sodium solvation number than NaDA. If one presumes that **2b** remains monomeric at all THF concentrations, these data would imply a monosolvated monomer, which contradicts significant accumulated experience.¹ We submit that the THF dependence (eq 2) in fact arises from dimer formation at low THF concentration. Unfortunately, solubility problems at low THF concentration prevented us from further probing this question.

Sodium Phenolate Structures.

Although it is not essential to elucidate the structures of the sodium phenolates (**3a–e**) to understand the Snieckus-Fries rearrangement, we sought to probe these structures owing to their role as intermediates in numerous pharmaceutical transformations en route to aryl ethers.¹⁷ There is also a general dearth of structural details on the solution structures of

organosodiums.² In short, a binary mixture of phenolates **3e** and **3f** displays no NMR spectroscopic evidence of heteroaggregation, indicating that they are monomeric. DFT computations with **3e** suggest that five-coordinate trisolvates (eq 3) are more stable.^{1c,18–20}

(3)

Kinetics and Mechanism of Orthometalation.

Tractable rates observed in the orthometalations of unsubstituted carbamates (assisted by the retarding effects of deuteration) allowed us to probe the mechanism of orthometalation in detail. Metalation of **1a-d₅** under second-order conditions (1.0 equiv NaDA) follows a decay with no anomalous curvatures that would have attested to autocatalysis or autoinhibition (Figure 3).²¹ Metalation of **1a-d₅** under pseudo-first-order conditions (0.010 M) at $-78\text{ }^{\circ}\text{C}$ by 0.10 M NaDA in 7.5 M THF/hexane follows a clean first-order decay (Figure 3, inset). At the completion of reaction, the baseline was zeroed and a second aliquot of substrate was added. The two pseudo-first-order rate constants (k_{obsd}) agree within 10%.

Plotting k_{obsd} vs THF concentration (Figure 4) and NaDA concentration (Figure 5) affords zeroth- and half-order dependencies, respectively. The downward drift in the THF dependence is only moderately disconcerting, displaying none of the curvature expected for a true inverse dependence. A routine control experiment^{1f} using 2,5-dimethyltetrahydrofuran (Me_2THF) instead of hexane as the cosolvent to maintain the polarity of the medium constant had no effect whatsoever; the downward drift does not *appear* to derive from secondary-shell (medium) effects. The idealized rate law²² (eq 4) and assignment of NaDA as tetrasolvated dimer **5^{1b}** are consistent with the generic mechanism in eq 5. A comparison of the rates of **1a** and **1a-d₅** ($k_{\text{H}}/k_{\text{D}}$ 6) confirms that proton transfer is rate limiting.

$$-\text{d}[\text{ArH}]/\text{d}t = k[\text{THF}]^0[\text{A}_2\text{S}_4]^{1/2}[\text{ArH}] \quad (4)$$

The stoichiometry of the transition structure²³ is consistent with a disolvated-monomer-based mechanism. DFT computations (using the ‘e’ series as noted above, Figure 6) confirm that transition structure **10** is computationally viable, with intrinsic reaction coordinate (IRC) calculations showing **11** as the first-formed product, which appears to rapidly collapse to the carbonyl-complexed form.²⁴

Mechanism of Snieckus-Fries Rearrangement.

Rearrangement of arylsodium **2a** to phenolate **3a** is an unobservable post-rate-limiting step (Scheme 2). By contrast, **2d** forms rapidly and rearranges slowly. Loss of **2d**, suggested to exist as a trisolvated monomer as described above, follows a first-order decay, manifests a first-order THF dependence with a considerable non-zero intercept (Figure 7), and shows no dependence on the concentration of excess NaDA (Figure 8). The idealized rate law (eq 6) is consistent with the generic mechanism in eqs 7 and eqs 8. DFT computations (staying with the 'e' series as noted above, Figure 9) afford a viable trisolvated transition structure **12**, but we could not locate a plausible tetrasolvate corresponding to **13**. Rate data for arylsodium **2f** point to an analogous mechanism.

$$-d[\text{ArNa}]/dt = (k + k'[\text{THF}]^1)[\text{ArNa}] \quad (6)$$

NaDA-Catalyzed Snieckus-Fries Rearrangement.

Rearrangement of fluoro-substituted arylsodium **2e** displays all of the accoutrements of a disolvated-monomer-based rearrangement. A slight inhibiting influence of THF is well within the norm for a zeroth-order dependence. A dependence on NaDA, however, was unexpected (Figure 10), as was the linearity indicating an apparent first-order rather than half-order dependence. In retrospect, perhaps this finding should not have come as a surprise, given that a similar LDA catalysis is observed for the Snieckus-Fries rearrangement of the aryllithium analog.^{7b}

The rate data for the NaDA catalyzed rearrangement implicates a mixed *trimer*-based transition structure containing two NaDA subunits. We computationally explored the roles of fleeting mixed dimers and mixed trimers to envision the mechanism and offer transition structures **14** and **15** as computationally viable models. A more highly solvated mixed trimer was not computationally viable. The energies were reasonable but are not isodesmic and should not be taken too seriously. Mixed trimer **15**, implicated by the rate studies, does not require that NaDA forfeit the full aggregation energy but, as drawn, requires forfeiting *three* solvent-sodium contacts from the $\text{ArNa}(\text{THF})_3/(\text{R}_2\text{NNA})_2(\text{THF})_4$ resting state at an estimated total energetic cost of 5 kcal/mol. (The third THF on the arylsodiums and fourth THF on NaDA are marginally stabilizing.) As a thought experiment, treating mixed dimers and mixed trimers (not shown) as independent groundstates, the barriers corresponding to **14** and **15** are of comparable energies.

Benzynes.

Arylsodiums and aryllithiums bearing halogen substituents may be susceptible to benzyne formation. Thus, while rearrangement of fluorinated arylsodium **2e** at 0 °C affords phenol **4e** in 79% isolated yield with no observable benzyne-derived products, rearrangement of the lithium analog of **2e**, generated using LDA, leads to low yields of **4e** along with **17**, **18**, and other debris consistent with benzyne **16**. Reaction of chlorinated arylsodium **2g** at –35 °C affords a low yield of phenol **4g** (<20%) along with benzyne-derived byproducts (Scheme 4).²⁵

The divergent chemoselectivities of the meta fluoro and chloro derivatives mimics the analogous lithium species. In aryllithiums, LiCl elimination is promoted by high solvent concentration and affiliated lack of a strong Li–Cl contact, whereas LiF elimination is favored by low solvent concentration, which promotes an Li–F contact.²⁶ Based on the propensity of **2e** to undergo rearrangement in lieu of elimination, we infer that the F–Na interaction is weak.

Summary and Conclusion

Synthetic chemists have exploited the Snieckus-Fries rearrangement as a means to achieve phenol ortho functionalization. The internal trapping mechanism also has probative mechanistic value. The overall reaction coordinate for the tandem orthometallation and subsequent Snieckus-Fries rearrangement is summarized in Scheme 5. Observable intermediates **2** and **3** appear to be di- or trisolvated monomers, as supported by DFT computations. Rate studies implicate the disolvated monomer-based transition structure **10** for the metalation and the tri- and possibly tetrasolvated monomer-based transition structures **12** and **13** for the rearrangement. Evidence of a NaDA-catalyzed rearrangement aligns with results from the corresponding lithium-based Snieckus-Fries rearrangement.

The overarching message is that the sodium analog of the Snieckus-Fries rearrangements works quite well. The orthometallations and rearrangements are markedly faster than their lithium analogs. As we explore the structure-reactivity-selectivity relationships in organosodium chemistry, we are pleased by how well the chemistry works and by the high solubilities of the sodium salts. Although we did detect aggregation effects of consequence, the generally lower frequency of occurrence in organosodium chemistry when compared to organolithium chemistry is refreshing and may render organosodium chemistry more predictable in the long run.

Experimental

Reagents and Solvents.

THF and hexane were distilled from blue or purple solutions containing sodium benzophenone ketyl. NaDA was prepared and isolated, although control experiments confirm that in situ-generated NaDA/DMEA/THF is indistinguishable. Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques. Aryl carbamates **1a–g** were prepared by literature procedures.⁶

IR spectroscopic analyses.

IR spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm⁻¹. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped by a septum for injections and a nitrogen line. After evacuation under full vacuum, heating, and flushing with nitrogen, the flask was charged with NaDA (64 mg, 0.10 mmol) in THF (5.0 mL) and cooled in a dry ice–acetone bath prepared with fresh acetone. After recording a background spectrum, we added aryl carbamate **1** (0.010 mmol) with stirring. For the most rapid reactions, IR spectra were recorded every 15 s with monitoring of the absorbance at 1730 cm⁻¹ over the course of the reaction.

NMR Spectroscopic Analyses.

NMR samples for reaction monitoring and structure determination were routinely prepared using stock solutions of NaDA in THF/hexane mixtures maintained at $-80\text{ }^{\circ}\text{C}$ and flame-sealed under partial vacuum. Standard ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on a 500 MHz spectrometer at 500 and 125.79 MHz, respectively. The ^1H and ^{13}C resonances were referenced to the CH_2O resonance (3.58 ppm) and CH_2O resonance (67.57 ppm) of THF at $-80\text{ }^{\circ}\text{C}$, respectively.

DFT Computations.

DFT calculations were carried out at the B3LYP/6–31G(d) level with single-point calculations at the M06–2X level of theory.^{10,11} Transition structures each had a single negative frequency.

2-Fluoro-6-hydroxy-*N,N*-diisopropylbenzamide (4e).

3-Fluorophenyl diisopropylcarbamate (**1c**, 479 mg, 2.0 mmol) in 5.0 mL THF was added dropwise over 10 minutes to a solution of NaDA (2.2 mmol, 271.0 mg) in THF (10.0 mL) at $-78\text{ }^{\circ}\text{C}$ under N_2 . The resulting solution was warmed to $0\text{ }^{\circ}\text{C}$, stirred for 2 h, and quenched with saturated aqueous ammonium chloride (8.0 mL). The THF was removed under reduced pressure and the aqueous residue was extracted with dichloromethane ($4\times 10\text{ mL}$). The combined organic extracts were dried (MgSO_4), filtered, and concentrated under reduced pressure to afford crude product, which was purified using flash column chromatography (8:1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$) to give **4e** (79%) as white needles. ^1H NMR (500 MHz, CDCl_3) δ 8.28 (1H, s), 7.15 (1H, dt, $J = 8.3, 6.6\text{ Hz}$), 6.75 (1H, dt, $J = 8.3, 0.8\text{ Hz}$), 6.58 (1H, ddd, $J = 9.3, 8.3, 1.0\text{ Hz}$), 3.70 (1H, s, br), 1.35 (12H, s, br). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, CDCl_3) δ 168.5, 158.5 (d, $J_{\text{C-F}} = 246.4\text{ Hz}$), 157.0 (d, $J_{\text{C-F}} = 6.4\text{ Hz}$), 132.6 (d, $J_{\text{C-F}} = 10.6\text{ Hz}$), 112.0 (d, $J_{\text{C-F}} = 6.4\text{ Hz}$), 106.8 (d, $J_{\text{C-F}} = 22.5\text{ Hz}$), 20.7. (The isopropyl methinyl carbon is missing owing to a conformational coalescence.) ^{19}F NMR (470.33 MHz, CDCl_3) δ -113.8. HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{FNO}_2$ 240.1399; Found 240.1390.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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24. Intrinsic reaction coordinate (IRC) calculations are defined as “the minimum energy reaction pathway (MERP) in mass-weighted cartesian coordinates between the transition state of a reaction and its reactants and products.” They show the minima preceding and following transition state.
25. The preference for the meta adduct 17 is consistent with literature reports and the developing stabilization of the arylsodium by either induction or chelation in the transition state. (a) Candito DA; Dobrovolsky D.; Lautens M. Development of an Intramolecular Aryne Ene Reaction and Application to the Formal Synthesis of (±)-Crinine. *J. Am. Chem. Soc* 2012, 134, 15572. [PubMed: 22906167] (b) Hickey MR; Allwein SP; Nelson TD; Kress MH; Sudah OS; Moment AJ; Rodgers SD; Kaba M; Fernandez P Process Development and Pilot Plant Synthesis of Methyl 2-Bromo-6-chlorobenzoate. *Org. Process Res. Dev* 2005, 9, 764.
26. (a) Ramírez A; Candler J; Bashore CG; Wirtz MC; Coe JW; Collum DB Formation of Benzyne from 2,6-Dihaloarylithiums: Mechanistic Basis of the Regioselectivity. *J. Am. Chem. Soc* 2004, 126, 14700. [PubMed: 15535677] (b) Riggs JC; Ramírez A; Cremeens ME; Bashore CG; Candler J; Wirtz MC; Coe JW; Collum DB Structural and Rate Studies of the Formation of Substituted Benzyne. *J. Am. Chem. Soc* 2008, 130, 3406. [PubMed: 18293971]

Figure 1.

IR spectrum for the metalation and rearrangement of 0.010 M diethylcarbamate **1b** with 0.15 M NaDA in 6.80 M THF/hexane at $-50\text{ }^{\circ}\text{C}$. The spectrum, recorded after 60 seconds, shows both arylsodium **2b** and phenolate **3b**.

Figure 2.

Plot of $[\text{ArNa}]/[\text{ArH}]$ versus $[\text{THF}]$ in hexane for the sodiation of diethylcarbamate **1b** (ArH) to give arylsodium **2b** (ArNa) at equilibrium with 0.10 M NaDA at -50°C . The curve represents an unweighted overtly simplified least-squares fit to $y = ax^b$ ($a = 8.1 \pm 0.7$, $b = -0.85 \pm 0.07$).

Figure 3.

Plot of phenyl- d_5 -dimethylcarbamate (**1a-d₅**) concentration versus time for the metalation of 0.10 M **1a-d₅** with 0.10 M NaDA in 7.5 M THF/hexane at $-78\text{ }^{\circ}\text{C}$. The curve represents an unweighted least-squares fit to the second-order function, $y = a/(1+bx) + c$ ($a = 0.1128 \pm 0.0002$, $b = -0.00010 \pm 0.00001$, $c = 0.014 \pm 0.001$). Insert: plot of phenyl- d_5 -dimethylcarbamate (**1a-d₅**) concentration versus time for the metalation of 0.010 M **1a-d₅** with 0.10 M NaDA in 7.5 M THF/hexane at $-78\text{ }^{\circ}\text{C}$. $y = ae^{bx} + c$ ($a = 0.034 \pm 0.001$, $b = 0.0012 \pm 0.0005$, $c = 0.0028 \pm 0.0001$).

Figure 4.

Plot of k_{obsd} versus $[\text{THF}]$ in hexane for the orthosodiation of carbamate **1a-d**₅ (0.010 M) by NaDA (0.10 M) at $-78\text{ }^{\circ}\text{C}$. The curve represents an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{THF}] + k'$ ($k = -1.8 \pm 0.4 \times 10^{-3}$, $k' = 2.9 \pm 0.3 \times 10^{-3}$).

Figure 5.

Plot of k_{obsd} versus [NaDA] in 6.2 M THF/hexane for the orthosodiation of carbamate **1a-d₅** (0.010 M) by NaDA at $-78\text{ }^{\circ}\text{C}$. The curve represents an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{NaDA}]^n$ ($k = 0.0044 \pm 0.0004$, $n = 0.55 \pm 0.06$).

Figure 6.
Computed transition structures for orthosodiation.

Figure 7.

Plot of k_{obsd} versus $[\text{THF}]$ in hexane cosolvent for the rearrangement of arylsodium **2d** (0.010 M) by NaDA (0.10 M) at $-15\text{ }^{\circ}\text{C}$. The curve represents an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{THF}]^n + k'$ ($k = 0.14 \pm 0.01 \times 10^{-3}$, $k' = 0.7 \pm 0.3 \times 10^{-3}$, $n = 1.17 \pm 0.04$)

Figure 8.

Plot of k_{obsd} versus $[\text{NaDA}]$ in 6.2 M THF/hexane for the rearrangement of arylsodium **2d** (0.010 M) at -15°C . The curve represents an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{NaDA}] + k'$ ($k = -0.9 \pm 0.1 \times 10^{-3}$, $k' = 1.7 \pm 0.1 \times 10^{-3}$)

Figure 9.
Computed transition structure of the Snieckus-Fries rearrangement.

Figure 10.

Plot of k_{obsd} versus $[\text{NaDA}]$ in 6.2 M THF/hexane for the rearrangement of arylsodium **2e** (0.010 M) at 0 °C. The curve represents an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{NaDA}]^n + k'$ ($k = 0.012 \pm 0.004$, $k' = 0.0012 \pm 0.0004$, $n = 1.15 \pm 0.03$)

- a**; R = Me, X = H (95%)
b; R = Et, X = H (86%)
c; R = *i*-Pr, X = H (80%)
d; R = *i*-Pr, X = OMe (85%)
e; R = *i*-Pr, X = F (79%)
f; R = *i*-Pr, X = CF₃ (82%)
g; R = *i*-Pr, X = Cl (<20%)

Scheme 1.

Orthometalation and Snieckus-Fries rearrangements of aryl carbamates with isolated yields.

Scheme 2.
Intermediate arylsodiums.

Scheme 3.
Computed structure of aryl sodium.

Scheme 4.
Benzyne formation.

Scheme 5.
Summary of structure and mechanism.