Why Does Kevlar Decompose, while Nomex Does Not, When Treated with Aqueous Chlorine Solutions?

Akin Akdag,[†] Hasan B. Kocer,[‡] S. D. Worley,*[,†] R. M. Broughton,[‡] T. R. Webb,[†] and Travis H. Bray[†]

Department of Chemistry and Biochemistry and Department of Polymer and Fiber Engineering, Auburn University, Auburn, Alabama 36849

Received: January 23, 2007; In Final Form: March 29, 2007

Kevlar and Nomex are high-performance polymers which have wide varieties of applications in daily life. Recently, they have been proposed to be biocidal materials when reacted with household bleach (sodium hypochlorite solution) because they contain amide moieties which can be chlorinated to generate biocidal *N*-halamine functional groups. Although Nomex can be chlorinated without any significant decomposition, Kevlar decomposes under the same chlorination conditions. In this study, two mimics for each of the polymers were synthesized to simulate the carboxylate and diaminophenylene components of the materials. It was found that the *p*-diaminophenylene component of the Kevlar mimic is oxidized to a quinone-type structure upon treatment with hypochlorous acid, which then decomposes. However, such a mechanism for the Nomex mimic is not possible. In this paper, based upon these observations, a plausible answer will be provided to the title question.

Introduction

N-Halamine chemistry has been a fruitful area of research since the late 1970s.[1] These compounds contain at least one nitrogen−halogen bond, where halogen generally refers to chlorine and bromine. The halogens have Pauling electronegativities (3.2 for Cl and 3.0 for Br) which are comparable to that for nitrogen (3.0); this renders halogens on *N*-halamines partially positively charged, thus oxidative.[2] The most important practical application for *N*-halamine compounds has been directed toward inactivation of pathogens. In other words, stable *N*-halamines are effective oxidizing agents that can oxidize the molecules on cell surfaces which are vital for cell survival.[3] Therefore, *N*-halamine chemistry has proved to be important in the development of effective antimicrobial compounds.[1−4]

Incoorparation of *N*-halamines into polymeric materials has provided a new avenue of research.[4] Such polymers can be used in a wide variety of applications, such as in textiles, coating materials, paints, water disinfectants, etc. Some examples such as those shown in Figure 1 were developed in these laboratories and elsewhere.[4]

Recent biological security threats have stimulated the exploration of new efficient ways to generate *N*-halamines. Sun and co-workers have pointed out that Nomex and Kevlar could be excellent candidates for incorporation of *N*-halamine functionality because their amide groups do not contain any α-hydrogens (e.g explicitly shown hydrogens on $R_2N\text{-}CH_2R$ are α-hydrogens), unlike Nylon derivatives (Figure 2).[5] That is, dehydrohalogenation cannot occur as a mechanism for the loss of biocidal efficacy. They have found that Nomex can be chlorinated sufficiently to inactivate microbial pathogens. On the other hand, they found that Kevlar, upon chlorination, decomposed. The chlorination of Nomex has been explored further by Sun and Broughton.[6] It was found that low chlorination loadings (Cl^+/amide) were due to the crystallinity of the Nomex. Therefore, low crystalline Nomex or Nomex blends were employed in order to generate high chlorination loadings. Since chlorination occurs on the surface of the fibers, it is understandable that later studies provided high chlorine percentage with increased surface area.[6] In these studies, the question to be addressed is: Why is Kevlar decomposed, but Nomex is chlorinated without decomposition, upon treatment with hypochlorus acid? The answer to this question could provide enlightenment to stimulate exploration of *N*-halamine chemistry for high-performance polymers. Sun and co-workers suggested that the decomposition of Kevlar upon attempted chlorination is due to the hydrolysis of the amide structure.[5] This work will attempt to address the matter through a study of four compounds which mimic portions of the Kevlar and Nomex structure.

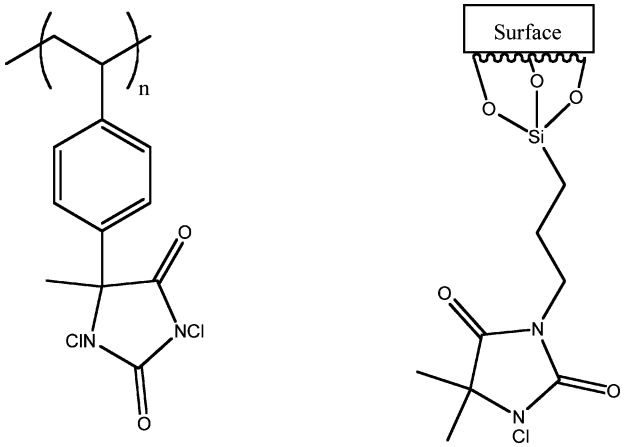


Figure 1. Two examples of polymeric *N*-halamines (adapted from ref 4).

The mimics were subjected to chlorination at various conditions with use of household bleach. The crystal structure of the

* Address correspondence to this author. Phone (334)844-6944. E-mail: worlesd@auburn.edu.
[†] Department of Chemistry and Biochemistry.
[‡] Department of Polymer and Fiber Engineering.

10.1021/jp070586c CCC: $37.00
Published on Web 04/28/2007

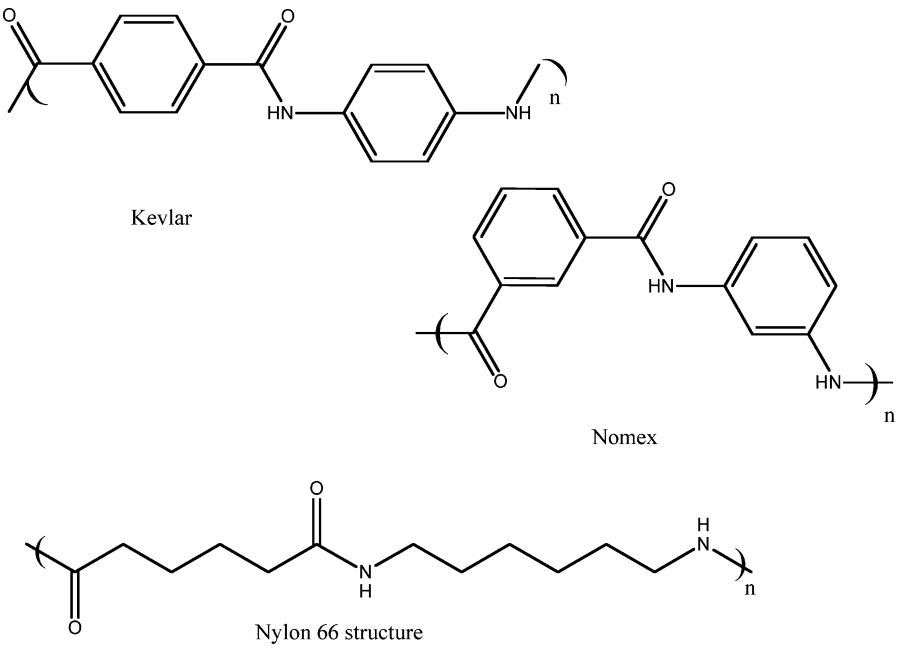
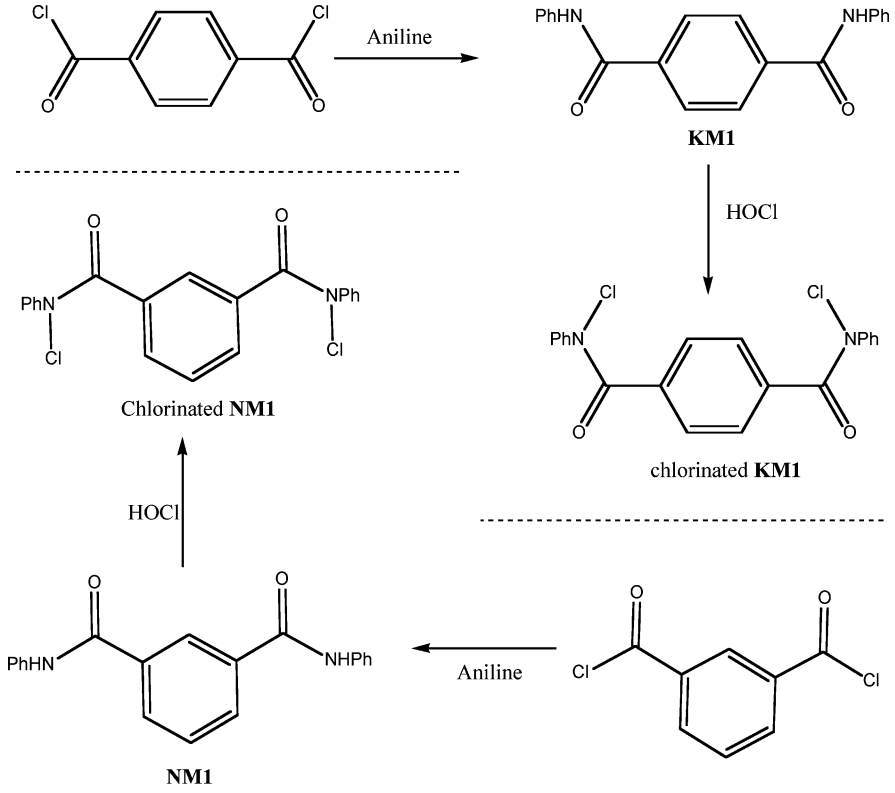


Figure 2. Structure of Kevlar, Nomex, and Nylon 66.

SCHEME 1: Synthesis of KM1, NM1, and Their Chlorinated Derivatives



chlorinated Nomex mimic was solved, and it was compared to a previously solved crystal structure of unchlorinated Nomex mimic. The crystal structure of the Kevlar mimic has been reported. On the basis of the information obtained, an explanation concerning the title question will be offered.

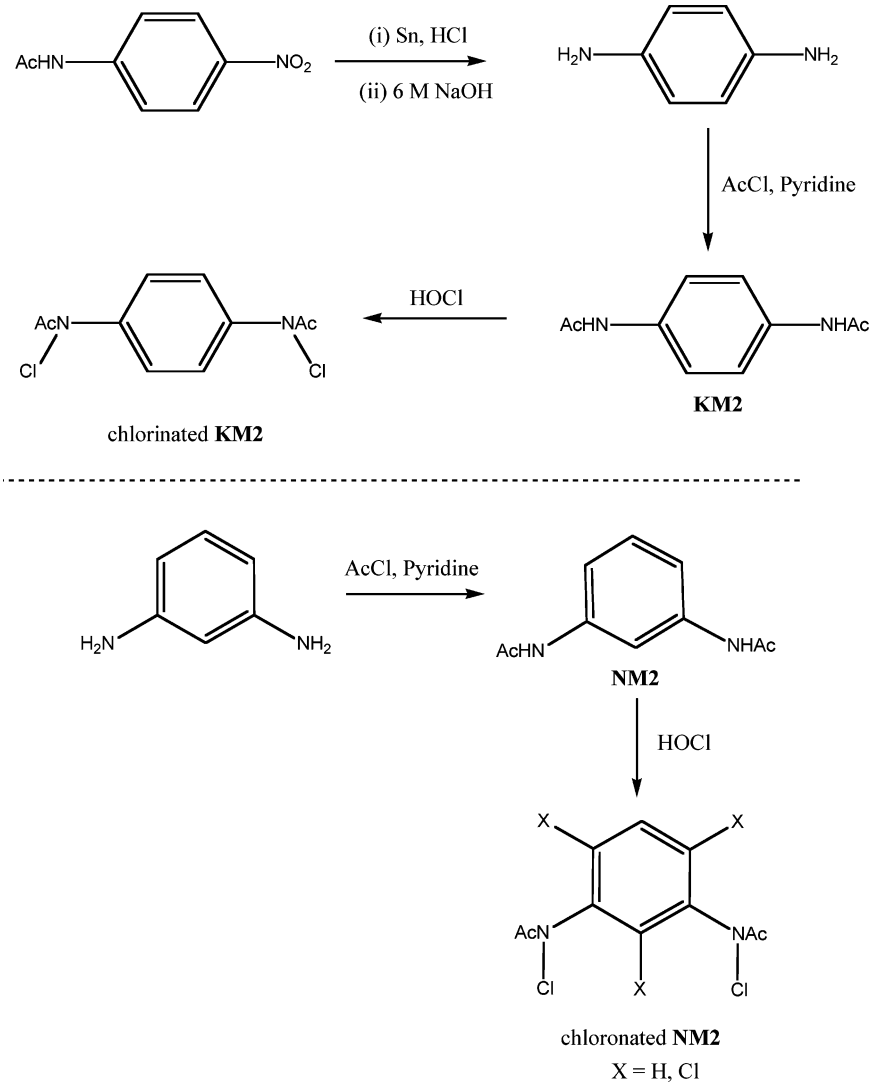
Experimental Section

General Procedure for KM1 and NM1 Synthesis (See Scheme 1). To a solution of aniline (2 mol equiv) in freshly distilled THF was added terephthaloyl chloride for **KM1** or isophthaloyl chloride for **NM1** (1 mol equiv). The mixture was stirred at room temperature for 4 h, and then the mixture was filtered and the resulting solid was washed with water and then with cold ethanol. The solids were dried in air to provide the corresponding materials.

N,N′-Diphenylterephthalamide (***KM1***): ^{1}H NMR (DMSO-d_6, 250 MHz) δ 10.39 (s, 2H), 8.10 (s, 4H), 7.80 (d, 4H), 7.38 (t, 4H), 7.13 (t, 2H). ^{13}C NMR (62.5 MHz) δ 165.28, 139.44, 137.93, 129.13, 128.19, 124.37, 120.95.

N,N′-Diphenylisophthalamide (***NM1***): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.41 (s, 2H), 8.59 (s, 1H), 8.18 (m, 2H), 7.84

SCHEME 2: Synthesis of KM2, NM2, and Their Chlorinated Derivatives



(m, 4H), 7.72 (m, 1H), 7.41 (m, 4H), 7.15 (m, 2H). ^{13}C NMR (100 MHz) δ 165.57, 139.56, 135.70, 131.15, 129.17, 129.11, 127.51, 124.32, 120.89.

Preparation of *p*-Phenylenediamine. To mixture of *p*-nitroacetanilide (1.8 g, 0.010 mol) in ethanol, prepared according to a literature procedure,[7] was added tin (2 g, 0.017 mol) and 10 mL of concentrated hydrochloric acid solution. The resulting mixture was refluxed for 4 h. Then the solvent was removed by evaporation, and the residue was dissolved in 100 mL of water with pH adjustment of the solution to 12 by addition of 6 M NaOH solution. This solution was extracted with *n*-butanol (4 × 50 mL), and combined organic phases were dried over anhydrous $MgSO_4$. Then the mixture was filtered, and the solvent was evaporated to provide *p*-aminoaniline, which was used in the next reaction step without further purification. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 6.39 (s, 4H), 4.51 (s, 4H). ^{13}C NMR (66.50 MHz) δ 139.07, 116.10.

General Procedure for the Synthesis of KM2 and NM2 (See Scheme 2). To a solution of the *p*-aminoaniline for **KM2** or *m*-aminoaniline for **NM2** (1 mol equiv) in freshly distilled THF was added pyridine (2 mol equiv). To this solution was added acetyl chloride (2 mol equiv) dropwise. The solution was stirred for 4 h, the solvent was evaporated, and the residue was dissolved in water and extracted with ethyl acetate. The combined organic phases were dried over anhydrous $MgSO_4$, which was removed by filtration. After evaporation of the solvent, the corresponding **KM2** and **NM2** were obtained.

N-(*4-Acetylaminophenyl*)*acetamide* (***KM2***): ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.86 (s, 2H), 7.48 (s, 4H), 2.02 (s, 6H). ^{13}C NMR (66.50 MHz) δ 168.37, 135.08, 119.81, 24.33.

N-(*3-Acetylaminophenyl*)*acetamide* (***NM2***): ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.94 (s, 2H), 7.89 (s, 1H), 7.20 (m, 3H) 2.04 (s, 6H). ^{13}C NMR (66.50 MHz) δ 168.75, 140.03, 129.20, 114.29, 110.24, 24.47.

Chlorination: Heterogeneous chlorination of the compounds was performed at 25 °C by using a 10% aqueous solution of commercially available household bleach, which contained 0.6% sodium hypochlorite; the pH of the solution was adjusted with 1 M HCl solution to the desired levels. The insoluble chlorinated products were removed by filtration and dried in air at ambient temperature. X-ray diffraction-quality crystals of chlorinated **NM1** were obtained by recrystallization from acetone and slow evaporation. Such crystals could not be obtained by this procedure for chlorinated **KM1**. The NMR data for the chlorinated compounds are given below (**Caution**! Do not use DMSO-d_6 as NMR solvent for *N*-halamines).

*Chlorinated **KM1***: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.20 (m). ^{13}C NMR (66.50 MHz) δ 167.27, 143.98, 135.43, 129.58, 128.99, 128.73, 128.12.

*Chlorinated **NM1***: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.20 (m). ^{13}C NMR (66.50 MHz) δ 167.18, 144.18, 133.45, 131.17, 129.83, 129.60, 128.89, 128.21, 127.97.

*Chlorinated **KM2***: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.51 (s, 4H), 2.23 (s, 6H). ^{13}C NMR (66.50 MHz) δ 168.82, 143.15, 128.95, 22.46.

*Chlorinated **NM2** (after 20 min of chlorination)*: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.50 (m, 4H), 2.23 (s, 6H). ^{13}C NMR (66.50 MHz) δ 168.88, 143.92, 130.58, 128.14, 127.16, 22.42.

*Chlorinated **NM2***: In this case there was not a single product (after 2 h of chlorination); therefore, the raw data for the mixture are given. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.50 (m), 2.23 (m). ^{13}C NMR (66.50 MHz) δ 168.97, 143.88, 142.45, 140.84, 131.56, 130.63, 130.10, 129.85, 128.20, 127.17, 22.42, 21.51.

Titration: The percentage of the oxidative chlorine as "Cl^+" was determined by iodometric titration, in which KI and starch were used as reactant and indicator, respectively, and $S_2O_3^{2-}$ as a reducing agent. The final $C1^+$ percent was calculated by using the following equation:

$$\% \, Cl^+ = \left(\frac{(N \times V) \times 35.45}{2 \times W} \right) \times 100$$

where N and V are the normality (equiv/L) and volume (L), respectively, of the $Na_2S_2O_3$ consumed in the titration, and W is the weight in grams of the sample.

Computational: All computations were performed with Gaussian03.[8] The B3LYP/6-311+G(2d,p) level of theory was employed for all of the theoretical predictions.

Results and Discussion

The focus of this work was to answer the following question: Why does Kevlar decompose, whereas Nomex does not when treated with aqueous bleach? This question was tackled by examining mimics for portions of the polymer structures. Two sets of the mimics of Kevlar and Nomex were synthesized. The first set of mimics was synthesized to understand the role of the terephthaloyl portion of the Kevlar polymer and the isophthaloyl portion of the Nomex polymer. The second set of mimics was synthesized to address the *p*-aminophenylene portion of the Kevlar and the *m*-aminophenylene portion of the Nomex.

The synthesis of the first set of the aromatic polyamides was straightforward. One equivalent of the terephthaloyl chloride (for **KM1**) or isophthaloyl chloride (for **NM1**) was reacted with 2 equiv of aniline in THF according to a literature procedure.[9] The air-dried **KM1** and **NM1** NMR spectra (^{1}H and ^{13}C in DMSO-d_6) were consistent with the published data. Although **KM1** was sparingly soluble in the NMR solvent, **NM1** dissolved completely. Moreover, we have observed that the **KM1** melting point (350 °C) was higher than the **NM1** melting point (290 °C). This suggests that intermolecular interactions among **KM1** molecules are stronger than those for the **NM1** molecules. It was decided to examine the X-ray crystal structures of the mimics to see if large differences could help address the title question.

The crystal structure of **KM1** was reported previously by Harkema et al.[10] The structure revealed that the molecule does not have C_s symmetry (i.e., it is not planar). The terminal phenyl groups are in the same plane, but not in the plane of the middle phenylene moiety. That is, the terminal phenyl groups are 68° out of the plane of the phenylene ring. Similarly, the carbonyl groups are out of the plane of the phenylene ring by 29°. The terminal phenyl groups are out of the plane of the N−H bonds by 20°. To increase intermolecular hydrogen bond efficiency in the crystal structure, the carbonyl moieties are out of the plane to both the phenylene and terminal phenyl groups.

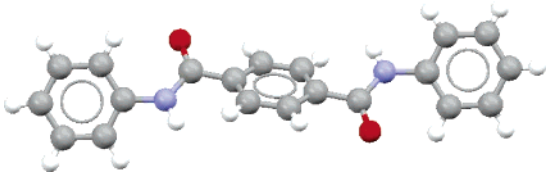


Figure 3. Crystal structure of **KM1**.

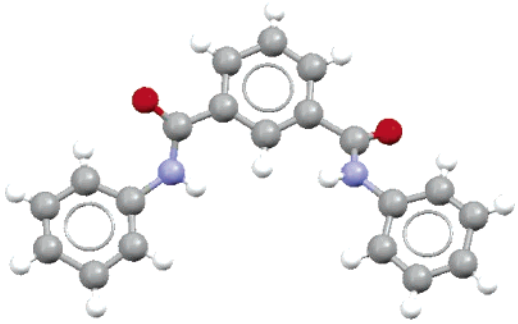


Figure 4. Crystal structure of **NM1**.

The **NM1** crystal structure was reported by Malone et al.[11] The crystal structure showed that the molecule is not planar (i.e., it has C_1 symmetry) in the solid state. The carbonyl moieties are out of the plane of the middle *m*-phenylene ring by 32° and 34°. Similarly, the N−H bonds are out of the phenylene ring plane by 24° and 29°. The terminal phenyl rings are not in the same plane as well, i.e., the planes are off from each other by 11°. The terminal phenyl groups are out of the plane of the adjacent N−H bonds by 26° and 34°. This conformation of the molecule in the solid state is necessitated in order to increase the efficiency of the intermolecular hydrogen bonding. There is no obvious difference in the crystal structures of the two mimics which can help answer the title question, although the DSC data for the two clearly indicate that the crystalline interaction is stronger for **KM1** (mp 350 °C) than for **NM1** (mp 290 °C).

When **NM1** was chlorinated by hypochlorous acid at a pH of about 8, a white solid was obtained. This solid was recrystallized in acetone by slow evaporation of the acetone. The crystal structure revealed that the terminal phenyl rings are bent over the middle of the phenylene ring. The carbonyl groups are out of the plane of the phenylene by 44° and 70°. In the crystal structure there is a close interaction between a carbonyl oxygen and one of the C−H's (para to the to C−N bond) of the terminal phenyl at a distance of 2.65 Å (the sum of van der Waals radii is 2.72 Å). There is also a $\pi-\pi$ interaction existing between the two phenylene rings on identical molecules which are related to each other by inversion. These interactions contribute to the crystal structure formation; however, in the **NM1** structure conventional hydrogen bonding contributed most to the crystal structure.

The N−Cl bond length on the chlorinated **NM1** was 1.70 Å. This bond length is consistent with previously calculated values.[2] Although a substantial difference in crystal structure for **NM1** occurs upon chlorination, there is no obvious reason for its ease of chlorination as compared to **KM1** for which diffraction-quality crystals could not be obtained.

The **KM1** and the **NM1** compounds can be chlorinated in dilute hypochlorous acid solutions. However, the **NM1** can be chlorinated at a higher rate than the **KM1**. The theoretical

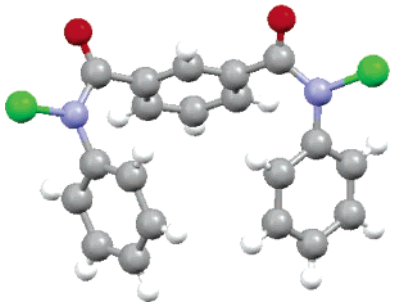


Figure 5. Crystal structure of chlorinated **NM1**.

oxidative chlorine percent (*ca.* 18%) can be attained at around pH 8 for **NM1**. On the other hand, pH 9 was necessary for the chlorination of **KM1**. This is because **NM1** is appreciably polar (computed dipole moment was 3.92 D), while **KM1** is nonpolar (computed dipole moment was 0.001 D). The dipole moments were predicted by a single-point calculation on the crystal structures published at the B3LYP/6-311+G(2d,p) level. Dipole moments affect the ability of molecules to interact with polar solvents like water; the more polar the molecule, the greater the interaction with water. Alkaline conditions are needed for **KM1** to be chlorinated efficiently due to the acidic proton on the amide moiety, which can be abstracted by hydroxide. Therefore, the ionized **KM1** specie can interact with the water and hypochlorus acid to proceed in chlorination. Even at ca. pH 9, the chlorination was extremely slow such that only 12% oxidative chlorine could be titrated after 140 h of chlorination. On the other hand, the **NM1** could be chlorinated up to 17% in less than 24 h. Therefore, from these percent conversions over much different time periods, it can be concluded that the degree of crystallinity, which is related to the ease of intermolecular hydrogen bonding and π-stacking, can affect the rate of *N*-chlorination by virtue of the polarity of the mimics interacting with aqueous HOCl. Of most importance to the title question, neither of the two mimics decomposed upon chlorination.

A DSC study of the chlorinated mimics showed that chlorinated **KM1** is less thermally stable than the chlorinated **NM1**. There is an exothermic DSC signal around 157 °C for the chlorinated **KM1**, but at 191 °C for the chlorinated **NM1**. When the chlorinated **NM1** was heated to 200 °C in vacuum for 45 min, it was observed by ^{1}H NMR that chlorine transferred to one of the terminal phenyl groups. This is similar to the Orton rearrangement observed for *N*-chloroacetanilide.[12]

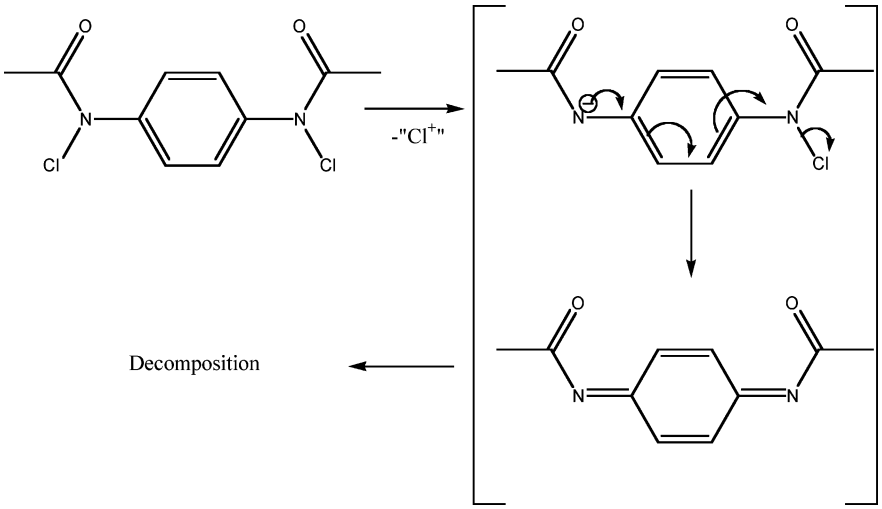
In summary, the first set of mimics has suggested that the stabilities of Kevlar and Nomex are not related to the carboxyl portions of the polymers as neither decomposes during chlorination. However, the carboxyl portions dictate the rates of chlorination due to the relative contributions to the crystallinity. It was also revealed that the chlorination of **NM1** forced it further out of plane to attain the observed crystal structure. Since the perturbation is less severe for the chlorinated **KM1**, these mimics cannot aid our understanding of why Kevlar decomposes upon chlorination.

The second set of mimics were synthesized to simulate the effect of the *p*-aminoaniline and *m*-aminoaniline portions of the Kevlar and Nomex, respectively. The syntheses of these mimics **KM2** and **NM2** were accomplished by treating the corresponding diaminophenylene with acetyl chloride in THF.[13] The NMR spectra of the compounds obtained were consistent with literature reports.[13]

The ^{1}H NMR spectrum of **KM2** showed three signals at 9.86, 7.48, and 2.02 ppm for N−H, C−H, and CH_3, respectively. The white colored **KM2** was chlorinated in a 10% bleach solution at ca. pH 7 for 20 min. The ^{1}H NMR spectrum of the chlorinated **KM2** showed that the N−H signal disappeared, with the two signals remaining at 7.51 ppm for the aromatic C−H and 2.23 ppm for the CH_3 protons. ^{13}C NMR spectra of the **KM2** and chlorinated **KM2** showed large shifts for the aromatic carbons: 135 → 143 ppm for the quaternary carbons, and 120 → 129 ppm for the other carbons (unchlorinated → chlorinated).

Over a time of 12 h, the solution of the chlorinated **KM2** changed from colorless to red, and the NMR spectra became markedly more complex (developing ^{1}H NMR signals at 1.75 and 4.84 ppm), indicating the formation of decomposition products. When a drop of water was added, the solution became a vivid orange/red after 12 h. The UV spectrum of the product mixture showed a λ_{max} at 2.65 nm, which was red-shifted by 10 nm from the corresponding λ_{max} in a sample of freshly chlorinated and colorless **KM2**. The IR spectrum of the sample mixture exhibited substantial losses in intensity of vibrational bands at 829 and 1565 cm^{-1} relative to that of **KM2**, which are characteristic of para-disubstituted aromatic rings. These observations lead us to propose the following mechanism: the chlorinated **KM2** with contact of water loses one of the chlorine atoms to form a negative charge which, when delocalized, leads to dissociation of the other chlorine to yield a quinone-type structure (see Scheme 3). Moreover, when the chlorinated **KM2** was suspended in distilled water, a red color appeared over 12 h. The resulting quinone-type structure is not stable and yields

SCHEME 3: Decompostion Mechanism for KM2



many byproducts based on literature reports.[14] Under dry conditions, the chlorinated **KM2** solid color turned light pink over the period of one week. In fact, the proposed structure in Scheme 3 has been prepared by oxidation of unchlorinated **KM2** with lead tetraacetate under dry conditions, and in its pure form, it was deep red with a UV λ_{max} at 2.80 nm.[14]

NM2 was also chlorinated under the same conditions as for **KM2**. The reaction conditions yielded the desired product as a light yellow solid. However, chlorination did not yield a solid when the reaction time was extended to 2 h. Therefore, the chlorination solution was extracted with ethyl acetate. The solvent was evaporated to give a yellow solid whose ^{1}H NMR spectrum showed that the N−H signal disappeared. However, the region for the CH_3 protons exhibited several new signals. The ^{13}C NMR spectrum of the chlorinated **NM2** showed two signals for the acetyl CH_3 carbon and 10 signals for the aromatic region. This suggests that the aromatic ring is chlorinated along with the formation of the N−Cl bond because there are three chlorination sites based on *ortho*−*para* directional ability of the acetanilide moieties on the *m*-phenylene ring. There are no other N−Cl decomposition mechanisms possible as for **KM2** except for the aromatic electrophilic substitution reactions and Orton rearrangement.

On the basis of the above observation, it can be suggested that **KM2** decomposes easily through oxidation of the phenylene rings to quinone-type structures and subsequent hydrolyzes. Therefore, we suggest that the *p*-aminoaniline moiety in the polymer Kevlar becomes a quinone-type structure upon chlorination. However, as mentioned earlier, this structure is not stable under moist conditions leading to decomposition of the polymer. On the other hand, chlorination of **NM2** revealed that such a mechanism is not possible for the Nomex polymer because of its meta substitution pattern, but it can undergo an Orton rearrangement and electrophilic aromatic substitution.

Conclusions

Many *N*-halamine structures have been incorporated into polymers. The quest for an easily obtainable polymer containing a chlorinated amide has led to work employing aromatic polyamide structures. However, it is known that Kevlar decomposes upon chlorination, while Nomex does not. This work has attempted to provide a rationalization for these observations.

Two sets of mimics were prepared to help attack the problem. A first set of mimics was synthesized to simulate the carboxyl moiety in the Nomex and Kevlar. A second set of mimics was prepared to model the *p*-diaminophenylene and *m*-diaminophenylene units of the Kevlar and Nomex.

It was shown that upon chlorination, the mimic **NM1** structurally underwent a large conformational change. The **NM1** crystal structure is dominated by intermolecular hydrogen bonding and $\pi-\pi$ interaction. The chlorinated **NM1** solid-state structure is dominated by C−H···O hydrogen bonding and $\pi-\pi$ interaction. The same is presumably true for **KM1**. Chlorination of the mimics **KM1** and **NM1** demonstrated that crystallinity affects the rate of chlorination. However, these changes cannot explain the decomposition mechanism for Kevlar.

The second set of mimics **KM2** and **NM2** were chlorinated by treating them with hypochlorous acid. It was observed that **KM2** was decomposed over time under moist conditions through a quinone-type intermediate. Although **NM2** could not undergo such a transformation, it was susceptible to aromatic electrophilic substitution reactions and Orton rearrangements. We suggest that the mechanism for decomposition of Kevlar upon chlorination is that shown in this work for the mimic **KM2**.

Acknowledgment. This work has been supported by the U.S. Air Force through contract F08637-02-C-7020 and the Halo-Source Company. The computation time was provided by the Alabama supercomputer. We would also like to thank Dr. T. Albrecht-Schmitt for helpful discussions concerning the single-crystal X-ray structure of chlorinated **NM1**.

Supporting Information Available: DSC plots for **KM1**, **NM1**, **KM2**, **NM2**, and their chlorinated derivatives; chlorination values for **KM1** and **NM1** at various pH values provided as graphs; chlorination versus time at their optimum pH values for **KM1** and **NM1**; crystallographic data for the chlorinated **NM1**; and the full citation for ref 8. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Worley, S. D.; Wojtowicz, J. A. *Kirk-Othmer Encycl. Chem. Technol., 4th Ed.* **2004**, 98−122. (b) Worley, S. D.; Sun, G. *Trends Polym. Sci.* (*Cambridge, U.K.*) **1996**, *4*, 364−370.

(2) Akdag, A.; Okur, S.; McKee, M. L.; Worley, S. D. *J. Chem. Theory Comput.* **2006**, *2*, 879−884.

(3) Kohl, H. H.; Wheatley, W. B.; Worley, S. D.; Bodor, N. *J. Pharm. Sci.* **1980**, *69*, 1292−1295.

(4) (a) Liang, J.; Chen, Y.; Barnes, K.; Wu, R.; Worley, S. D.; Huang, T.-S. *Biomaterials* **2006**, *27*, 2495−2501. (b) Sun, G.; Wheatley, W. B.; Worley, S. D. *Ind. Eng. Chem. Res.* **1994**, *33*, 168−170. (c) Sun, Y.; Sun, G. *J. Appl. Polym. Sci.* **2003**, *88*, 1032−1039. (d) Sun, Y.; Sun, G. *Macromolecules* **2002**, *35*, 8909−8912. (e) Makal, U.; Wood, L.; Ohman, D.; Wynne, K. J. *Biomaterials* **2006**, *27*, 1316−1326.

(5) Sun, Y.; Sun, G. *Ind. Eng. Chem. Res.* **2004**, *43*, 5015−5020.

(6) (a) Sun, G.; Sun, Y.; Morshed, M. *Abstracts of Papers*; 227th National Meeting of the American Chemical Society, Anaheim, CA, March 2006; American Chemical Society: Washington, DC, 2006; CELL-135 (b) Lee, J.; Broughton, R. M.; Worley, S. D.; Huang, T. S.; Fan, X. *Abstracts of Papers*; 232nd National Meeting of the American Chemical Society; San Francisco, CA, September 2006; American Chemical Society: Washington, DC, 2006; CELL-009. (c) Sun, G.; Sandstrom, A. *Abstracts of Papers*; 231st National Meeting of the American Chemical Society; Atlanta, GA, March 2006; American Chemical Society: Washington, DC, 2006; CELL-022.

(7) Suzuki, H.; Tatsumi, A.; Ishibashi, T.; Mori, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 339−343.

(8) Frisch, M. J.; et al. *Gaussian03*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2004 (for full citation see the Supporting Information).

(9) (a) Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675−1683. (b) Kavallieratos, K.; de Gala, S. R.; Austin, D. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 2325−2326. (c) Sellarajah, S.; Lekishvili, T.; Bowring, C.; Thompsett, A. R.; Rudyk, H.; Birkett, C. R.; Brown, D. R.; Gilbert, I. H. *J. Med. Chem.* **2004**, *47*, 5515−5534.

(10) Harkema, S.; Gaymans, R. J.; van Hummel, G. J.; Zylberlicht, D. *Acta Cryst.* **1979**, *B35*, 506−508.

(11) Malone, J. F.; Murray, C. M.; Dolan, G. M.; Docherty, R.; Lavery, A. J. *Chem. Mater.* **1997**, *9*, 2983−2989.

(12) (a) King, H.; Orton, K. J. P. *J. Chem. Soc. Trans.* **1911**, *99*, 1377−1382. (b) Underwood, G. R.; Dietze, P. E. *J. Org. Chem.* **1984**, *49*, 5225−5229.

(13) (a) De Renzi, A.; Panunzi, A.; Saporito, A.; Vitagliano, A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1095−1098. (b) Dzierzbicka, K.; Trzonkowskim P.; Sewerynek, P.; Myliwski, A. *J. Med. Chem.* **2003**, *46*, 978−986.

(14) (a) Adams, R.; Anderson, J. L. *J. Am. Chem. Soc.*, **72**, 5154−5157. (b) Avdeenko, A. P.; Marchenko, I. L. *Russ. J. Org. Chem.* **2001**, *37*, 822−829.