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## The Stabilities of N–Cl Bonds in Biocidal Materials

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**Abstract:** N-halamine chemistry has been a research topic of considerable importance in these laboratories for over two decades. N-halamine compounds are useful in preparing biocidal materials. There are three N–Cl moieties available in cyclic N-halamine compounds: imide, amide, and amine. The stabilities toward the release of free halogen have been experimentally shown to decrease in the order amine > amide > imide. In this work, this generalization has been tested theoretically at the level of B3LYP/6-31+G(d) and using the conductor-like polarizable continuum aqueous solvation model with UAKS cavities. Excellent accord was observed between theory and experiment. It was also found that the imide and amide N-halamine stabilities on hydantoin rings could be reversed with substitution patterns at the 5 position.

### Introduction

Compounds containing nitrogen–halogen (N-halamine) bonds have been shown to be excellent biocides.<sup>1</sup> N-halamines act as sources of free halogens, which are potent oxidizing agents.<sup>2</sup> The oxidations in a cellular system lead to the destruction of microorganisms in a direct contact mechanism.<sup>1b</sup>

Numerous N-halamine compounds have been synthesized in these laboratories over the past 25 years.<sup>3</sup> These compounds have been incorporated into macromolecules (e.g., polymers) and surfaces (e.g., textiles).<sup>4</sup> The goal of the work has been to develop stable biocidal compounds which do not lose their oxidative chlorine contents readily in the presence of water and organics.<sup>3b</sup>

In principle, there are three types of N-halamine structures possible: imide, amide, and amine. The stabilities of these to hydrolysis and reactions with organic receptors vary.<sup>5</sup> The reaction of a general N-halamine with water to give the amine, amide, or imide and hypochlorous acid is given in eq 1.



The dissociation constants for different N-halamine functionalities are given in Table 1.<sup>6</sup> The table shows that the

**Table 1.** N-Halamine Dissociation Constants in Aqueous Solution

nature of N-halamine	dissociation constant
imide	$<10^{-4}$
amide	$<10^{-9}$
amine	$<10^{-12}$

stabilities toward dissociation of the N–Cl moieties are in the order amine > amide > imide halamine.

As previously mentioned, Worley and co-workers have demonstrated that many examples of N-halamine compounds are efficient biocides. The kinetics of inactivation of the bacteria depend on the nature of the N–Cl moiety. The higher the dissociation constant, the more rapid is the biocidal action. For example, an N-halamine containing an imide N–Cl functionality kills bacteria more rapidly than the one which has an amide N–Cl functionality.<sup>7</sup> However, the stability (i.e., the persistence) of the N-halamine is important because the presence of the N-halamine is necessary for preventing the re-establishment of the microbes.

Some examples of the potential precursor N-halamine compounds synthesized and studied in these laboratories are 5,5-dimethylhydantoin (DMH) derivatives,<sup>8</sup> 2,2,5,5-tetramethylimidazolidinone (TMIO),<sup>9</sup> and 7,7,9,9-tetramethyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (TTDD).<sup>10</sup> As seen from the structures in Figure 1, DMH has an imide and an

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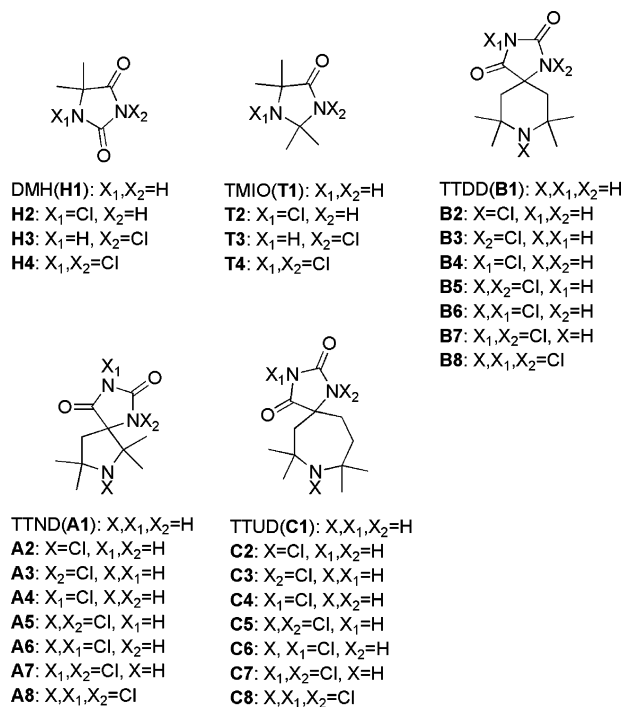


Figure 1. Structures of the compounds under study.

amide functionality, TMIO has an amide and an amine functionality, and TTDD has an imide, an amide, and an amine functionality. All of the above compounds, when chlorinated, gave N-halamine compounds which acted as excellent biocides.

In this study, we seek to determine natures of the effects which are playing an important role in N-halamine stabilities. The chlorinated forms of DMH and TMIO were first subjected to the high-level calculations in order to see if the theoretical results were in accord with the experimental ones. Then, TTDD (**B**) and its five-membered (**A**) and seven-membered (**C**) ring analogues were subjected to the high-level calculations to examine the effect of ring size on chlorine stability. This study may lead to new classes of more effective N-halamine compounds.

## Computational Details

All calculations were performed with Gaussian 03.<sup>11</sup> The structures were optimized at the B3LYP/3-21G level initially, and then, optimized structures were subjected to reoptimization at the B3LYP/6-31+G(d) level. The zero-point and thermal corrections were calculated at the B3LYP/6-31+G(d) level. Natural bond order (NBO) analyses were performed on the geometry obtained at the B3LYP/6-31+G(d) level for **H4** and **T4**. Solvation effects were included in the geometry obtained at the B3LYP/6-31+G(d) level with the conductor-like polarizable continuum model (CPCM) using UAKS cavities.<sup>12</sup> The free energy of the reaction was computed using eq 2:

$$\Delta G(\text{solution phase}) = \Delta G(\text{gas phase}) - \Delta G(\text{solvation of products}) + \Delta G(\text{solvation of reactants}) \quad (2)$$

A 1.9 kcal/mol correction was included in the calculation due to the fact that the molecules are changing in state from

Table 2. Total Energies, Enthalpies, and Free Energies for **H**, **T**, **A**, **B**, and **C** Series<sup>a</sup>

compound	$H(298\text{ K})$ (Hartree)	$G(g)$ (Hartree)	$\Delta G(sol)$ (kcal/mol)
<b>H1</b>	-455.223 389	-455.264 681	-16.75
<b>H2</b>	-914.776 951	-914.823 284	-9.88
<b>H3</b>	-914.775 843	-914.820 889	-11.04
<b>H4</b>	-1374.328 763	-1374.378 716	-2.30
<b>T1</b>	-459.720 398	-459.767 615	-10.71
<b>T2</b>	-919.282 827	-919.333 251	-7.56
<b>T3</b>	-919.279 877	-919.330 134	-4.94
<b>T4</b>	-1378.838 750	-1378.893 926	-0.33
<b>A1</b>	-705.785 633	-705.841 811	-16.60
<b>A2</b>	-1165.351 218	-1165.409 885	-13.72
<b>A3</b>	-1165.332 984	-1165.392 420	-12.11
<b>A4</b>	-1165.338 243	-1165.397 807	-10.43
<b>A5</b>	-1624.898 869	-1624.961 326	-8.36
<b>A6</b>	-1624.903 655	-1624.966 109	-7.11
<b>A7</b>	-1624.884 749	-1624.948 239	-4.45
<b>A8</b>	-2084.450 284	-2084.516 704	-0.41
<b>A3-i</b>	-1165.332 954	-1165.392 008	-11.97
<b>B1</b>	-745.068 831	-745.125 335	-18.53
<b>B2</b>	-1204.631 788	-1204.691 205	-16.92
<b>B3</b>	-1204.611 948	-1204.673 655	-13.31
<b>B4</b>	-1204.621 193	-1204.681 226	-12.47
<b>B5</b>	-1664.173 875	-1664.238 753	-11.20
<b>B6</b>	-1664.183 867	-1664.247 180	-10.62
<b>B7</b>	-1664.163 577	-1664.228 836	-5.96
<b>B8</b>	-2123.725 767	-2123.792 423	-4.40
<b>B3-i</b>	-1204.618 544	-1204.677 658	-11.22
<b>C1</b>	-784.345 708	-784.406 077	-16.71
<b>C2</b>	-1243.898 694	-1243.962 430	-15.68
<b>C3</b>	-1243.889 753	-1243.953 061	-11.45
<b>C4</b>	-1243.898 666	-1243.962 906	-10.48
<b>C5</b>	-1703.444 025	-1703.510 128	-10.28
<b>C6</b>	-1703.451 343	-1703.519 069	-9.31
<b>C7</b>	-1703.441 668	-1703.508 536	-4.03
<b>C8</b>	-2162.995 817	-2163.065 856	-2.67
<b>C3-i</b>	-1243.891 450	-1243.953 361	-11.13

<sup>a</sup> Total energies are at the B3LYP/6-31+G(d)//B3LYP/6-31+G(d) level; thermal corrections are made at the B3LYP/6-31+G(d) level, and solvation corrections are made at the CPCM/B3LYP/6-31+G(d) level.

an ideal gas (1 mol/22.4 L at 298 K) to an ideal solution (1 mol/L).<sup>13</sup> A correction factor of 2.4 kcal/mol was also applied due to the fact that the water molarity is 55.56.<sup>13</sup> All of the results are tabulated in Table 2. In order to check the reliability of the DFT relative energies, calculations were also carried out at the MP4SDQT/6-31+G(d)//B3LYP/6-31+G(d) level for **H1–H4**. Free energies of reactions using MP4SDQT/6-31+G(d) energies are reported in Table 3 for reactions involving **H1–H4** with HOCl and H<sub>2</sub>O.

## Results and Discussion

**5,5-Dimethylhydantoin (DMH).** 5,5-Dimethylhydantoin contains two nitrogen atoms, which can be halogenated to give two different N-halamine moieties. Experimentally, it was shown that an imide halamine is more labile than an amide one.<sup>14</sup> Theoretically, the same pattern was observed (see Table 2). The calculations showed that the bond length for the imide N-halamine is shorter than that for the amide

**Table 3.** Free Energies (kcal/mol) in the Gas Phase and in Solution for Selected Reactions at the B3LYP/6-31+G(d) Level

eq	reaction	B3LYP/6-31+G(d)//B3LYP/6-31+G(d) <sup>a</sup>		MP4SDQT/6-31+G(d)//B3LYP/6-31+G(d) <sup>a</sup>	
		$\Delta G(\text{gas})$	$\Delta G(\text{aq})$	$\Delta G(\text{gas})$	$\Delta G(\text{aq})$
3	<b>H1</b> + HOCl → <b>H2</b> + H <sub>2</sub> O	−9.71	−2.16	−14.39	−6.84
4	<b>H1</b> + HOCl → <b>H3</b> + H <sub>2</sub> O	−8.21	−1.82	−11.67	−5.28
5	<b>H4</b> + H <sub>2</sub> O → <b>H2</b> + HOCl	7.72	−0.54	11.56	3.30
6	<b>H4</b> + H <sub>2</sub> O → <b>H3</b> + HOCl	9.23	−0.19	14.28	4.86
7	<b>T1</b> + HOCl → <b>T2</b> + H <sub>2</sub> O	−14.35	−10.52		
8	<b>T1</b> + HOCl → <b>T3</b> + H <sub>2</sub> O	−12.17	−5.72		
9	<b>T4</b> + H <sub>2</sub> O → <b>T2</b> + HOCl	11.01	3.10		
10	<b>T4</b> + H <sub>2</sub> O → <b>T3</b> + HOCl	12.97	7.68		
11	<b>A1</b> + HOCl → <b>A3</b> + H <sub>2</sub> O	−4.70	0.47		
12	<b>A1</b> + HOCl → <b>A4</b> + H <sub>2</sub> O	−8.08	−1.23		
13	<b>A2</b> + HOCl → <b>A5</b> + H <sub>2</sub> O	−5.22	0.82		
14	<b>A2</b> + HOCl → <b>A6</b> + H <sub>2</sub> O	−8.22	−0.93		
15	<b>B1</b> + HOCl → <b>B3</b> + H <sub>2</sub> O	−3.26	2.64		
16	<b>B1</b> + HOCl → <b>B4</b> + H <sub>2</sub> O	−8.01	−1.27		
17	<b>B2</b> + HOCl → <b>B5</b> + H <sub>2</sub> O	−2.78	3.62		
18	<b>B2</b> + HOCl → <b>B6</b> + H <sub>2</sub> O	−8.06	−1.08		
19	<b>C1</b> + HOCl → <b>C3</b> + H <sub>2</sub> O	−2.42	3.52		
20	<b>C1</b> + HOCl → <b>C4</b> + H <sub>2</sub> O	−8.60	−1.69		
21	<b>C2</b> + HOCl → <b>C5</b> + H <sub>2</sub> O	−2.87	3.21		
22	<b>C2</b> + HOCl → <b>C6</b> + H <sub>2</sub> O	−8.48	−1.43		

<sup>a</sup> Zero-point energy, heat capacity, and entropy corrections to 298 K were made at the B3LYP/6-31+G(d) level. Solvation effects in water were determined at the CPCM/B3LYP/6-31+G(d) level with UAKS cavities at B3LYP/6-31+G(d) optimized geometries.

N-halamine (1.70 and 1.72 Å, respectively) in both isolated systems (**H2** and **H3**) and the combined system (**H4**). The experimental value for the N–Cl bond length in N-chlorosuccinimide is 1.69 Å, and an amide N-halamine N–Cl bond length is 1.71 Å in N-chloroazasteroids,<sup>15</sup> in excellent accord with the computations. Although the N–Cl bond length for the imide is, in fact, shorter than that for the amide, the amide N–Cl bond is clearly stronger, as evidenced by both experimental and computational data. This could be due to the increased polarity of the imide N–Cl bond over the amide one, leading to more-ionic character in the former and more-rapid dissociation by hydrolysis.

When **H1** is subjected to a reaction with hypochlorous acid in water, the formation of **H2** is more spontaneous and exothermic than is the formation of **H3**. To test the idea that the imide N-halamine chlorine is first to dissociate, the reaction of **H4** with water was treated computationally. It was found that forming the amide N-halamine **H2** is more favorable than forming imide N-halamine **H3** (eqs 3–6). The order of N-halamine stability in the gas phase and in solution (water as solvent) did not change. However, the Gibbs free energy differences between reaction 3 and reaction 4 decreased by 1.16 kcal/mol when solvation was included. This decrease arises from the solvation differences of **H1** and **H2**. Thus, the computational methods were in accord with experimental observations for the hydantoin derivatives in that the formation of **H2** was predicted to occur more spontaneously than that of **H3**.

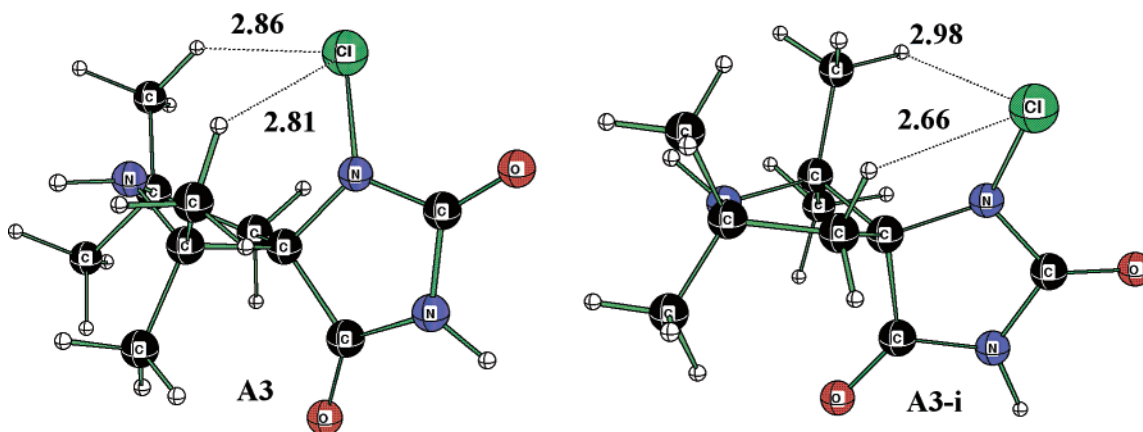
**2,2,5,5-Tetramethylimidazolidin-4-one (TMIO).** TMIO has a hindered secondary amine and an amide functional group, and when chlorinated, both functional groups have been shown experimentally to bind chlorine more tightly than does DMH.<sup>16</sup> It was demonstrated that the amine N-halamine group bound chlorine more strongly than did the amide

N-halamine group (Table 2). Moreover, experiments showed that the monohalogenation of the title compound produced the amide N-halamine as the kinetically controlled product, which rearranges to the thermodynamically controlled product of the amine N-halamine over time.<sup>17</sup> Surprisingly, the N–Cl bond lengths calculated for the amide and the amine were 1.73 and 1.77 Å, respectively.

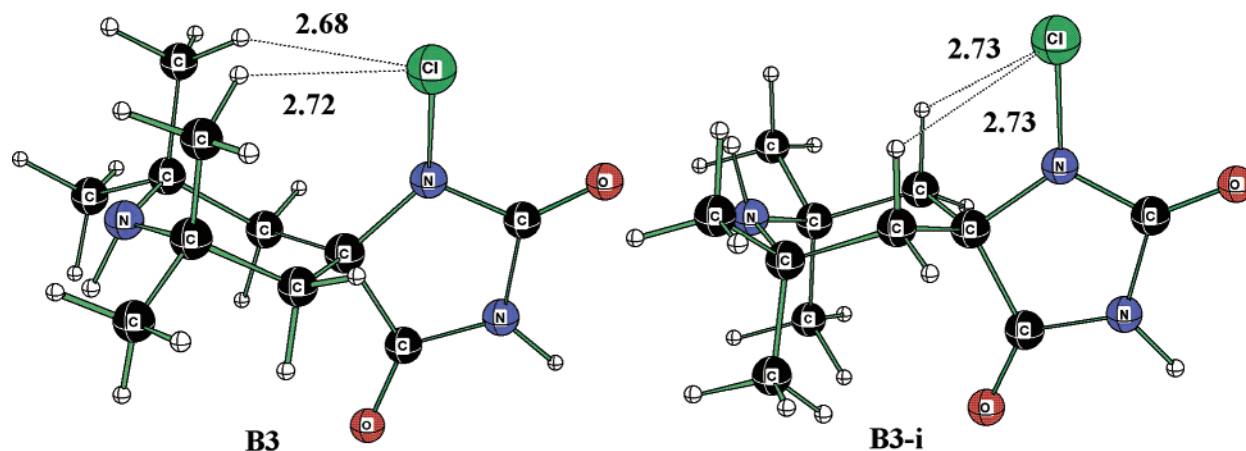
As seen in Table 2, the amide N-chloramine **T3** was predicted to be higher in energy than the amine **T2**. The reactions examined in eqs 7–10 show that the reaction forming **T2** is more favored than the one forming **T3** thermodynamically and that the order did not change with the addition of solvation.

The free energy of solvation for **T2** and **T3** shows a 2.62 kcal/mol difference. This difference is due to the fact that the amide is more polarized than the amine.

**The Spiro Systems (A, B, C). 6,6,8,8-Tetramethyl-1,3,7-triazaspiro[4.4]nonane-2,4-dione.** On the basis of the experimental and the theoretical results for DMH and TMIO, similar results were expected for the order of stabilities for N-halamines of the **A** structure. However, Table 2 shows that the order is amine > imide > amide N-halamine in terms of stability. The reversal between amide and imide has been a focal point of the analysis. As seen in Figure 2, steric interaction between methyl groups and chlorine seems to affect the stability of an amide N-halamine group. The distances between the chlorine and hydrogens on the methyl group are the reason for this steric hindrance. It was expected that changing **A3** to **A3-i** (the conformation has been changed, see Figure 2) would alter the N-halamine stability order. But, it was observed that the stability order did not change. Furthermore, inverting the pyrrolidine ring with respect to the hydantoin ring caused a negligible increase in energy, enthalpy, and free energy (**A3** → **A3-i**).



**Figure 2.** Minimized structures at the B3LYP/6-31+G(d) level of **A3** and **A3-i**.



**Figure 3.** Minimized structures at the B3LYP/6-31+G(d) level of **B3** and **B3-i**.

The N–Cl bond lengths are similar to those for DMH and TMIO. The amine has the longest bond length at 1.77 Å, then the amide at 1.71 Å, and then the imide at 1.70 Å. Thus, as discussed earlier, the N–Cl bond length becomes shorter as the bond polarity increases.

The energy difference between **A3** and **A4** is 3.34 kcal/mol and that for **A5** and **A6** is 2.94 kcal/mol. The chlorination reaction thermodynamics showed the same pattern in gas and aqueous solution (eqs 11–14).

**7,7,9,9-Tetramethyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione.** From an energetic point of view, the order of N-halamine stability is the same as that for the **A** series: amine > imide > amide. This order was largely affected by the steric interactions between chlorine connected to the amide nitrogen and the methyl groups (see Figure 3). The distance between chlorine and the methyl groups for the **B** series is even smaller than that for the **A** and is within the range of 2.62–2.72 Å. These shorter distances can be rationalized from 1 to 3 diaxial interactions (six-membered ring in the chair conformation).

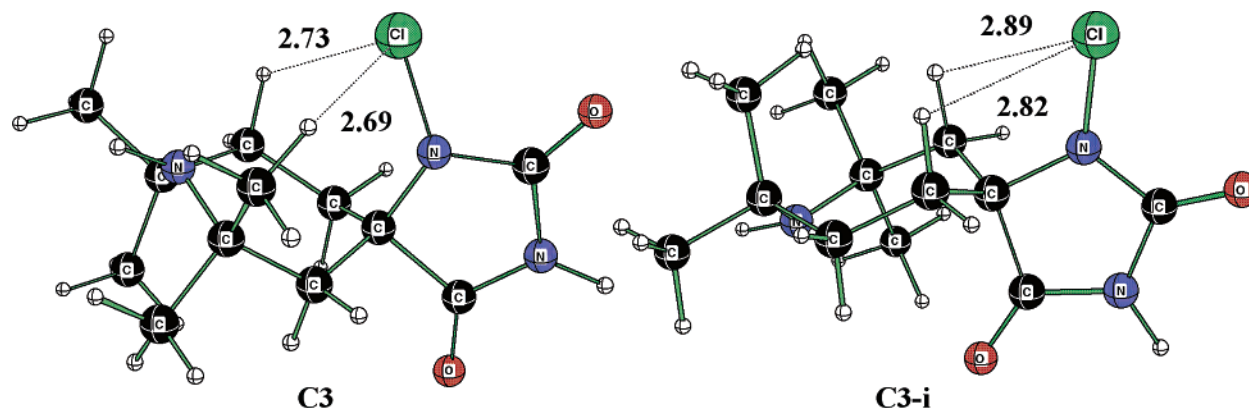
The **B3** was inverted to **B3-i** (see Figure 3); that is, the amide functionality was brought to the equatorial position. It was seen that 1–3 diaxial interaction between methyl groups and chlorine has diminished because of the chair conformation of the piperidine moiety. Although the amide N-halamine stability has been affected by steric interaction with the methyl group, the energy was not low

enough to be more stable than the imide N-halamine. Because the amide N-halamine chlorine is above the ring, inevitable steric interactions with hydrogens on the axial position occur.

The analysis of data for the **B** series (see Table 2) showed the same pattern as that for the **A** series. **B4** is thermodynamically more stable than **B3**, and similarly, **B6** is more stable than **B5**. Furthermore, the reactions of **B1** and **B2** with hypochlorous acid showed that the imide N-halamine is formed more spontaneously than is the amide N-halamine, both in the gas phase and in water (eqs 15–18).

**7,7,9,9-Tetramethyl-1,3,8-triaza-spiro[4.6]undecane-2,4-dione.** The same pattern was observed for the **C** series as in the cases of the **A** and **B** series (see Table 2). The reason for the amide N-halamine being less stable than the imide N-halamine appears to be due to steric hindrance in the case of the **C** series overall. The distance between the amine chlorine and one methyl group was observed to be within the range of 2.67–2.69 Å. Even though the methyl group for one side (methyl on the 7 position) is far enough away to not have significant steric interactions, it was seen that the chlorine is too close to a hydrogen on the ring (distance is changing from 2.70 to 2.73 Å), as in Figure 4. Therefore, the same procedure was followed as above; the ring was inverted. The inversion process caused the energy to become lower, but not enough to be lower than that for **C4**.





**Figure 4.** Minimized structures at the B3LYP/6-31+G(d) level of **C3** and **C3-i**.

It was expected that, by relaxing the ring (larger ring systems), the steric effect would decrease. Thus, the amide N-halamine could become more stable than the imide N-halamine. To test this hypothesis, a seven-membered ring has been attached to the 5 position of the hydantoin. Despite the initial expectations, it was shown that imide N-halamine is still more stable than the amide N-halamine (Table 2). The reactions for the **C** series showed the same order as that in cases of the **A** and **B** series in terms of spontaneity, both in the gas and solution phases (eqs 19–22).

As seen for the cases of **A**, **B**, and **C**, the N-halamine stability is not only determined by the electronic effects but is also determined by the substituents at the 5 position of the hydantoin ring. The effect of the substituents seems to be steric, with electronic effects being less important. The conformation of the cyclic systems at the 5 position affects the stability of the amide N-halamine from a steric point of view.

As alluded to earlier, the N–Cl bond lengths for the N-halamines showed an interesting pattern: amine(N–Cl) > amide(N–Cl) > imide(N–Cl). The NBO analysis for **H4** and **T4** showed that the hybridization of the nitrogen atom remains the same in all nitrogen cases. However, the natural population charges differ. For **H4**, the imide nitrogen has a charge of  $-0.54$  (the Cl bonded to this nitrogen has a charge of  $0.23$ ) and the amide nitrogen has a charge of  $-0.52$  (the Cl has a charge of  $0.18$ ). For **T4**, the amide nitrogen has a charge of  $-0.51$  (for Cl, it is  $0.18$ ) and the amine nitrogen has a charge of  $-0.50$  (Cl has  $0.08$ ). This polarization agrees with a literature report.<sup>18</sup> Moreover, the Wiberg bond orders are consistent with the bond lengths. As a result, the imide bond is more polarized than the amide, which is more polarized than the amine. The higher bond polarization causes the shorter bond length because of Coulombic attraction.

## Conclusions

In this study, N-halamines were investigated theoretically. It was shown that the experimental stability order could be reproduced with high-level calculations both in the gas phase and in solution. However, the polar N–Cl bonds have the higher solvation energy.

The calculated N–Cl bond length was surprising in that the strongest bond as evidenced by ease of hydrolytic dissociations, amine(N–Cl) > amide(N–Cl) > imide(N–

Cl), was the longest bond. It could be concluded that the greater the ionic character of the bond, the shorter was the bond length.

The steric effect of cyclic moieties at the 5 position of the hydantoin ring causes the amide N-halamine moiety to be more labile than the imide N-halamine one for the **A**, **B**, and **C** series. Varying the ring sizes does not affect the amine N-halamine stability in the ranking.

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**Note Added after ASAP Publication.** This article was released ASAP on March 16, 2006, with the incorrect Received Date. The correct version was posted on April 12, 2006.

**Supporting Information Available:** The optimized gas-phase structures and Cartesian coordinates of **H**, **T**, **A**, **B**, and **C** series at the B3LYP/6-31+G(d) level are given. The absolute energies at the B3LYP/3-21G and B3LYP/6-31+(G) levels, zero-point energies, enthalpy corrections, entropies, and solvation energies were tabulated for **H**, **T**, **A**, **B**, **C**, water, and hypochlorous acid. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (2) The term “free halogen” refers to a halogen with an oxidation state of +1. In water, this forms hypohalous acid or the hypohalite anion depending upon pH.
- (3) For example: (a) Tsao, T.-C.; Williams, D. E.; Worley, C. G.; Worley, S. D. *Biotechnol. Prog.* **1991**, *7*, 60–66. (b) Worley, S. D.; Williams, D. E.; Barnela, S. B. *Water Res.* **1987**, *21*, 983–988.
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