Mechanism of Formation of Biocidal Imidazolidin-4-one Derivatives: An Ab Initio Density-Functional Theory Study

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N-halamine chemistry has been a research topic of considerable importance in these laboratories for over 2 decades because N-halamine compounds are very useful in preparing biocidal materials. To understand the utility of these compounds, the stabilities and mechanism of halogenation of cyclic N-halamine compounds should be resolved. The important precursor biocidal compound, 2,2,5,5-tetramethylimidazolidin-4-one (TMIO) was considered as a model in this theoretical study. The thermodynamic and kinetic products of monohalogenation were investigated along with tautomerization of TMIO and succinimide theoretically at the level of B3LYP/6-311+G(2d,p). Solvation effects (water and chloroform) were included using the CPCM solvation model with UAKS cavities. Several mechanisms have been proposed for the chlorine migration from the 3-position (kinetic product) to the 1-position (thermodynamic product) of the TMIO ring. The results are in agreement with experimental NMR data.

Introduction

Compounds containing nitrogen−halogen bonds are excellent biocides.[1] They act as oxidizing agents whose actions inactivate the microorganisms. This phenomenon occurs by one of two mechanisms:[2] through dissociation to free halogen in solution or through direct transfer of halogen to the biological receptor. The former results from the transfer of halogen from polar N−X bonds to water, generating halogen in the "+1" oxidation state as hypochlorous acid or hypochlorite anions. For the other method, the halogen is directly transferred to the biological receptor, which occurs with less polar N−X bonds, to form a thermodynamically more stable species. Although both methods are effective, the latter mechanism is more effective in some cases in preventing regeneration of microorganisms because of the presence of the stable N-halamine compound in solution.[3]

Work in these laboratories has proceeded concerning the development of novel heterocyclic biocidal N-halamine derivatives, which have long-term stabilities in contact with aqueous solution as well as in dry storage.[4] It was shown that cyclic amines, such as oxazolidinones, imidazolidinones, hydantoins, and spirocyclic amines can function for the aforementioned purposes (see Figure 1).[5] Moreover, it was shown that the nature of the nitrogen, bonded to halogen, is important in terms of the N-halamine stability which can be rationilized as the more polar the groups attached to the nitrogen, the less stable the N-halamine in aqueous medium toward hydrolysis of these compounds.[6]

In previous studies, it was observed that unless there is a steric hindrance factor, imide N-halamine moieties are less stable than amide N-halamine ones, which in turn are less stable than the amine N-halamine moieties.[7] This stability trend has provided a general idea of an ideal biocidal material depending on the purpose. For example, if there is need for a biocide to inactivate microorganisms rapidly, then imide N-halamine compounds should be used. However, if there is a need for long-term stability in order to prevent the reestablishment of microbes, then amine N-halamines are the best choice.[3]

The halogenation of heterocyclic compounds with excess halogen provides the N-halamines.[8] When 5,5-dimethylhydantoin is chlorinated, 1,3-dichloro-5,5-dimethylhydantoin is obtained. Likewise, in the presence of excess free chlorine, 2,2,5,5-tetramethylimidazolidin-4-one (**T,** TMIO) gives 1,3-dichloro-2,2,5,5-tetramethylimidazolidin-4-one (**T4**). When these compounds were treated with 1 equiv of the halogenation agent, an interesting phenomenon was observed. For the hydantoin ring system, it was observed experimentally that the imide N-halamine was first produced, then over time it rearranged to the amide N-halamine in water.[9] The imide N-halamine was termed as the kinetic product, and the amide N-halamine was referred to as the thermodynamic product. Similarly, for the imidazolidinone derivative **T**, amide N-halamine was the kinetic product, and amine N-halamine was the thermodynamic product in chloroform solvent (see Scheme 1).[9]

In this study, the mechanism of chlorination of the TMIO (**T**) with hypochlorous acid and N-chlorosuccinimide (NCS) was investigated theoretically both in the gas and solution phases. Although experimentally it was observed that the amide N-halamine was the kinetic product and the amine N-halamine was the thermodynamic product, the course of this rearrangement was not clear. We now have evidence in the course of this investigation that tautomerization of TMIO and succinimide are involved.

Computational Methods

All calculations were performed with Gaussian 03.[10] The structures were optimized at the B3LYP/6-311+G(2d,p) level and zero-point and thermal corrections were calculated at the same level. Solvation effects were included with CPCM using UAKS cavities.[11] The free energy of the reaction was computed using eq 1. A 1.9 kcal/mol correction was included in the

$$\Delta G(\text{solution}) = \Delta G(\text{gas}) + \Delta G(\text{solvation}) \qquad (1)$$

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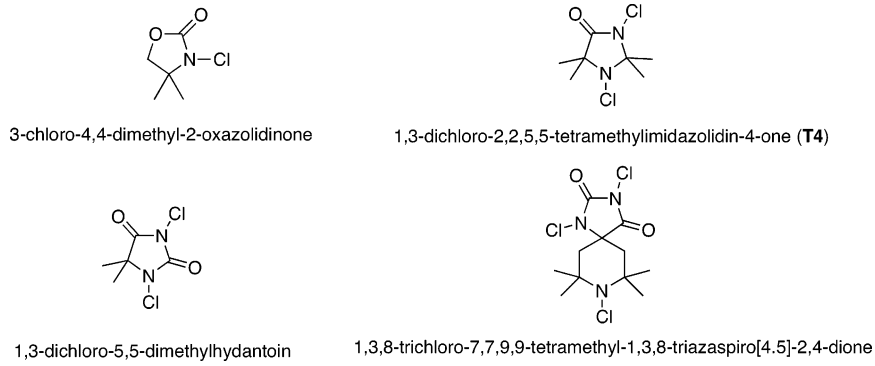


Figure 1. Examples of stable N-chloramines.

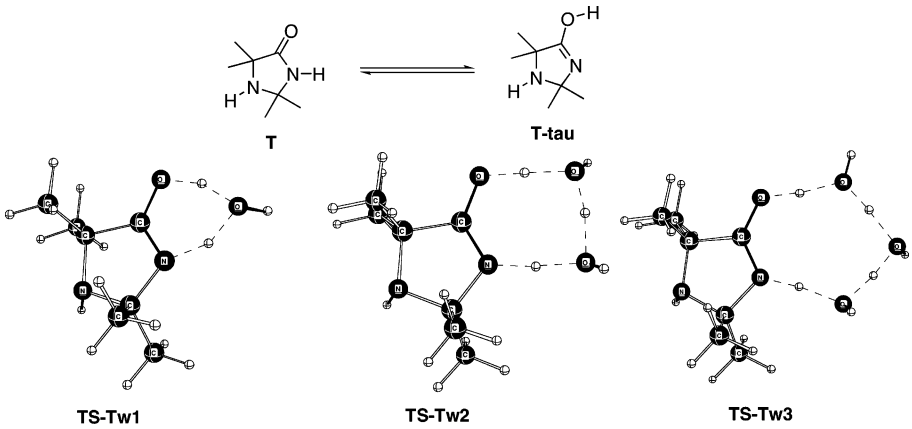
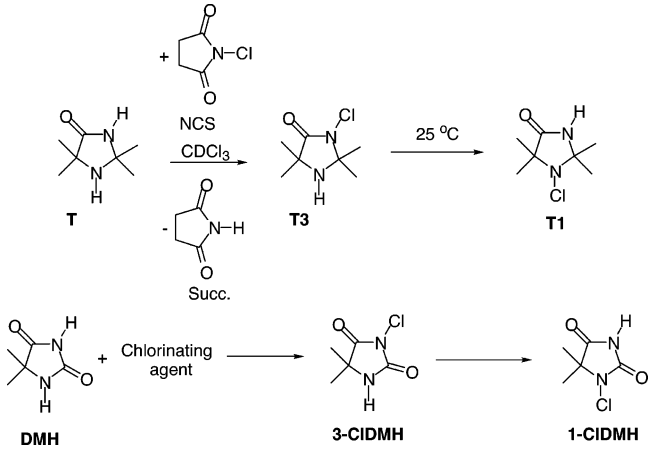


Figure 2. Tautomerization of **T** in water. Transition state structures for one-water, two-water and three-water cases.

SCHEME 1: Experimentally Observed Monochlorination of TMIO (T) and 5,5-dimethylhydantoin (DMH)



calculation because the molecules are changing in state from ideal gas (1 mol/24.4 L) to ideal solution (1 mol/L) at 298 K.[12] A correction factor of 2.40 kcal/mol was also applied to reactions in liquid water because the water molarity is 55.56.[12]

Results and Discussion

Stability of N-Halamines. To understand the chlorine stability (Table 1) on any N-chloramine, one should investigate the mechanism of chlorination. Previously, a concerted mechanism was postulated for formation of an amide N-halamine.[13] Therefore, a concerted mechanism for the chlorination of **T** with hypochlorous acid in water and with N-chlorosuccinimide in chloroform was studied. For the formation of **T3**, tautomerization of TMIO was crucial. Therefore, tautomerization is discussed first in this article both in the gas and solution phases.

TABLE 1: The Relative Energies, Enthalpies, and Free Energies (kcal/mol) at 298 K for T1 and T3

	ΔE	ΔH	ΔG(g)	ΔG(aq)	$\Delta G(CHCl_3)$
T1	0.00	0.00	0.00	0.00	0.00
T3	1.22	1.65	1.78	4.59	2.81

TABLE 2: Relative Energies for Tautomerization of T in Water

	ΔE	ΔH	ΔG(g)	ΔG(aq)
T + H_2O	0.00	0.00	0.00	0.00
TS−Tw1	11.73	8.64	20.04	30.25
T-tau + H_2O	12.22	11.90	12.01	15.55
T + $2H_2O$	0.00	0.00	0.00	0.00
T + $(H_2O)_2$	−4.69	−4.29	3.33	0.30
TS−Tw2	−1.74	−4.69	16.94	30.32
T-tau + $2H_2O$	12.22	11.90	12.01	15.55
T + $3H_2O$	0.00	0.00	0.00	0.00
T + $(H_2O)_3$	−16.48	−12.66	4.13	6.70
TS−Tw3	−6.36	−9.00	21.72	37.39
T-tau + $3H_2O$	12.22	11.90	12.01	15.55

Tautomerization of T in Water. Proton transfer from the amide nitrogen of TMIO (**T**) to oxygen was investigated in water via a one-, two-, and three-water bridge (see Figure 2). As seen in Table 2, the mechanism involving two waters in the gas phase is more favorable than the three and one water cases. However, when aqueous solvation is included, tautomerizations through the one-water and two-water bridges become very close in free energy (30.25 and 30.32 kcal/mol, respectively) and slightly more favorable than through the three-water bridge (37.39 kcal/mol). A literature survey showed that tautomerization of amides should occur in one of three ways; through intramolecular proton shift, through proton exchange in a dimer, or by water assisted proton transfer. [14] The first two cases of the literature were not

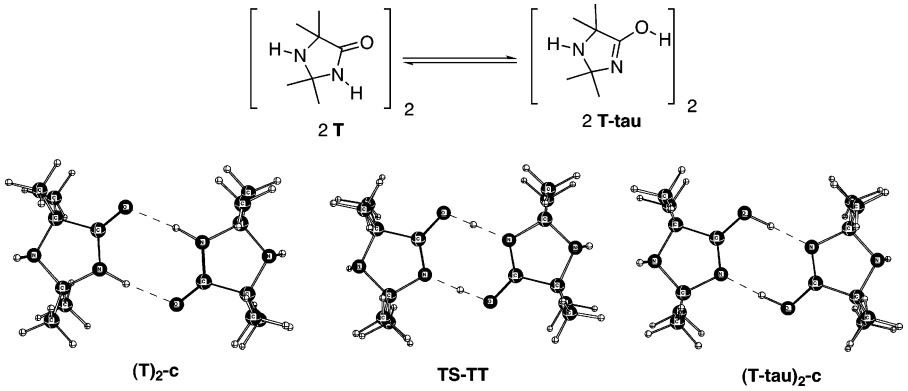


Figure 3. Tautomerization of **T** in chloroform.

TABLE 3: Relative Energies of Tautomerization of T and Succinimide in Chloroform

	ΔE	ΔH	ΔG(g)	ΔG($CHCl_3$)
T + **T**	0.00	0.00	0.00	0.00
(T)$_2$−c	−14.34	−13.17	−2.85	6.02
TS−TT	4.04	0.19	12.75	18.07
(T-tau)$_2$−c	3.31	3.10	14.90	24.82
T-tau + **T-tau**	24.43	23.79	24.02	28.00
T + H_2O	0.00	0.00	0.00	0.00[a]
TS−Tw1	11.73	8.64	20.04	24.27
T-tau + H_2O	12.22	11.90	12.01	14.00[a]
succ + H_2O	0.00	0.00	0.00	0.00[a]
TS−sw1	13.85	11.19	22.39	24.79
succ-tau + H_2O	17.19	17.04	16.84	15.91[a]
succ + succ	0.00	0.00	0.00	0.00
TS−ss	9.64	6.77	19.41	24.40
succ-tau + succ-tau	34.38	34.08	33.69	31.83

[a] Change of state correction (2.40 kcal/mol) not made for bulk water.

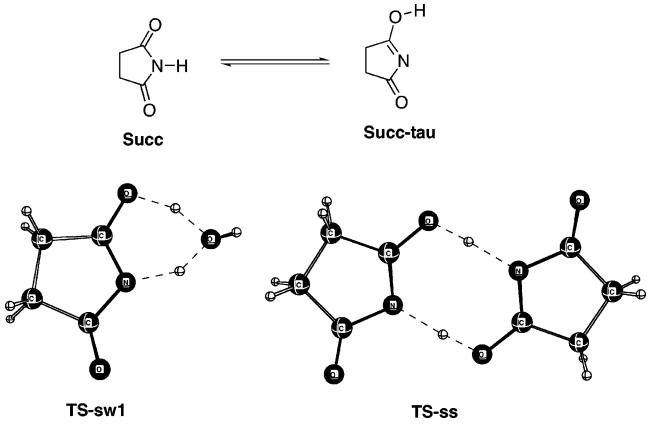


Figure 4. Tautomerization of succinimide in chloroform.

considered to occur in water. Therefore, the water molecules were involved in the proton-transfer process.

Tautomerization in Chloroform. In chloroform, tautomerization of **T** is proposed via two concerted proton transfers in the dimer (**TS−TT**, Figure 3). We investigated the reactant complex (**(T)$_2$−c**) and the product complex (**(T-tau)$_2$−c**); the transition state was 12.05 kcal/mol higher in free energy than **(T)$_2$−c** but 6.75 kcal/mol lower than **(T-tau)$_2$−c**. One difficulty with this mechanism is that formation of two higher-energy tautomers is required.

Since no special effort was made to exclude water from the reaction, the water present in chloroform can act as a catalyst in the tautomerization. Such a mechanism was proposed[15] in the cis → trans isomerization of HN═NH in water and may operate in the present mechanism. With one water, the free-energy barrier is 24.27 kcal/mol (**TS−Tw1**, Figure 2 and Table 3).

Tautomerization of Succinimide in Chloroform. Studies of tautomerization of succinimide showed a similar situation as was observed for tautomerization of **T** in chloroform, in which tautomerization through a dimeric structure has a transition state lower in energy than are the energies of the products when solvation is taken into account (see Table 3). This problem led to an idea that catalytic water might be involved in the tautomerization of succinimide (Figure 4).

Mechanism of Formation of T3 and T1 in Aqueous Solution with HOCl. One mechanism for the formation of **T1** involves two water molecules and a hypochlorous acid molecule. In the transition state (**TS1w2**), while chlorine on hypochlorous acid is transferred to the hindered amine, the hydroxyl group abstracts a proton from the neighboring water, which in turn abstracts a proton from the other water molecule, which abstracts the amine proton (Figure 5a). This is a concerted process and has a free-energy barrier of 33.62 kcal/mol in water.

For the chlorination of the amide nitrogen, a similar transition state (**TS3w2**) as for the formation of **T1** was proposed (Figure 5b). When this transition state was optimized, a proton shift was observed to form the enol form of the amide. It is known that protonation of amides occurs at the carbonyl moiety;[16] thus, the transition state was accepted as the transition state for the formation of **T3**. In other words, first the **T** tautomerizes to the **T-tau** structure, which undergoes a chlorination with hypochlorous acid. While the nitrogen lone pair attacks the chlorine, the hydroxyl group abstracts a proton from the next water, which then abstracts the proton from the last water participating in the mechanism (Figure 5a). After the last water donates its proton, it abstracts the proton on the tautomerized amide to form **T3** and three water molecules. As a result, **T** is chlorinated via forming **T-tau**, to form **T3** in a two-step manner. Consequently, the chlorination requires 35.36 kcal/mol.

Out of two possible products, **T1** and **T3**, the formation of **T3** is kinetically driven because of the lower activation barrier, and the formation of **T1** is thermodynamically driven because of the lower energy in the gas phase. Although **T3** is the kinetic product in the gas phase, **T1** is the kinetically and thermodynamically favored product in solution. This result is due to the fact that amides are more polarized than the amines. Thus amides possess more hydration free energy than do the amines.

It was observed that the formation of the transition states **TS1w2** and **TS3w2** (Figure 5) are exothermic for the two-water molecules system (Table 4). It was interesting to point out that the barriers are completely entropic. Thus, the transition state has a negative enthalpy with respect to reactants, but a positive Gibbs free energy.

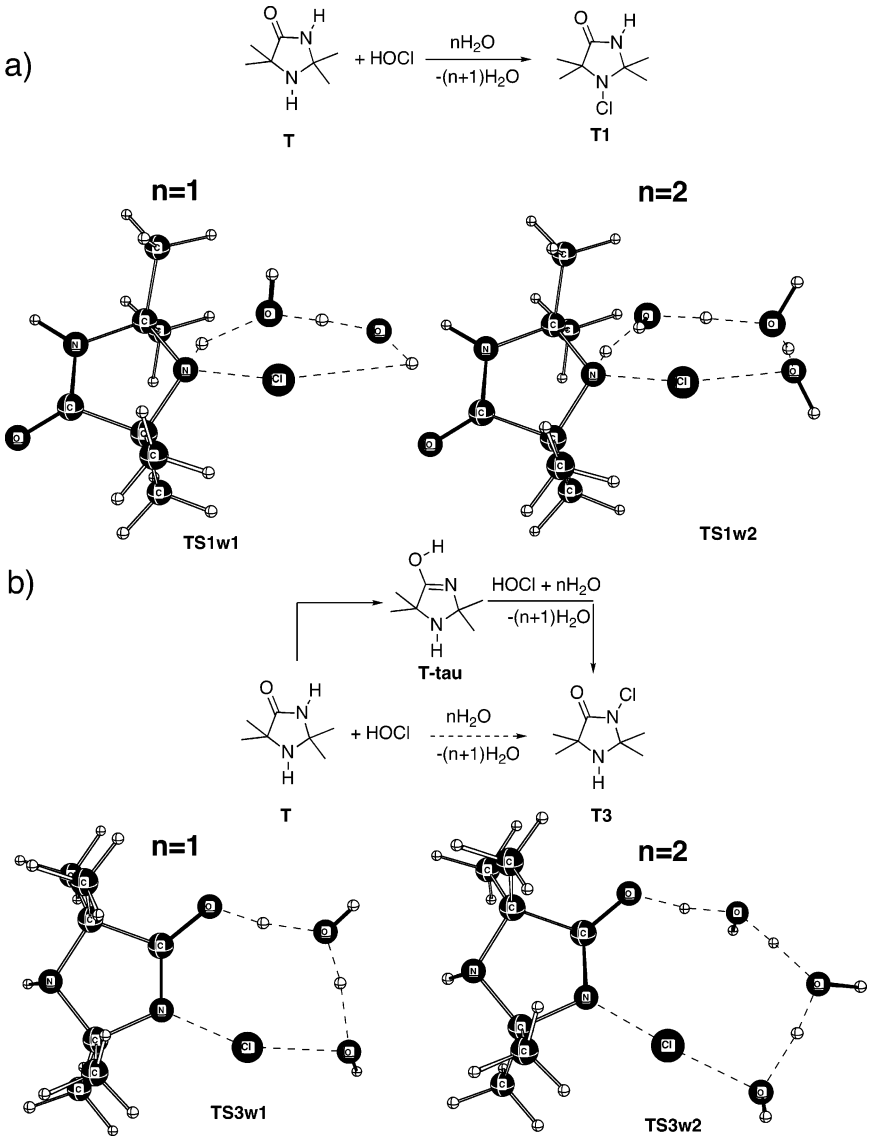


Figure 5. (a) Formation of **T1** from **T** with hypochlorous acid and one or two water molecules; (b) transition state structures for the chlorination of **T** to yield **T3** using one or two water molecules.

TABLE 4: The Relative Energies, Enthalpies, and Free Energies in kcal/mol at 298 K (Gas Phase, Aqueous Solution) for the Transition State for Formation of T1 and T3 from T, Hypochlorous Acid, and Two Water Molecules

	ΔE	ΔH	ΔG(g)	ΔG(aq)
T + $2H_2O$ + HOCl	0.00	0.00	0.00	0.00
T-tau + $2H_2O$ + HOCl	12.22	11.90	12.01	15.55
T + $(H_2O)_2$ + HOCl	−4.69	−4.29	3.33	0.30
T-tau + $(H_2O)_2$ + HOCl	7.53	7.61	15.33	15.84
TS1w2 (T → T1)	−3.94	−4.39	28.74	33.62
TS3w2 (T → T3)	−9.96	−10.67	22.34	35.36
T1 + $3H_2O$	−16.46	−17.50	−16.13	−12.40
T3 + $3H_2O$	−15.24	−15.86	−14.35	−7.81
T1 + $(H_2O)_3$	−32.95	−30.17	−11.99	−5.69
T3 + $(H_2O)_3$	−31.72	−28.52	−10.21	−1.10

As seen in Table 5, the chlorination reactions involving one water molecule pass through a barrier which has both enthalpic and entropic contributions, making this mechanism less likely as compared to the mechanism involving two water molecules (see Figure 5 for transition state structures).

Mechanism of Formation of T3 and T1 in the Presence of N-Chlorosuccinimide. Likewise, the chlorination with N-chlorosuccinimide was also investigated in a concerted mechanism. As seen in Table 6, **T3** formation is favored kinetically, but **T1** is the thermodynamic product. Unlike chlorination with hypochlorous acid, the addition of free energy of solvation did not change the preference. The solvation did not change the preferences of formation and stability order of product in chloroform. This is in agreement with prior experimental results.

TABLE 5: The Relative Energies, Enthalpies, and Free Energies in kcal/mol at 298 K (Gas Phase and Aqueous Solution) for the Formation of T1 and T3 Involving One Water Molecule

	ΔE	ΔH	ΔG(g)	ΔG(aq)
T + H_2O + HOCl	0.00	0.00	0.00	0.00
T-tau + H_2O + HOCl	12.22	11.90	12.01	15.55
TS1w1 (T → T1)	24.25	23.66	45.67	44.39
TS3w1 (T → T3)	3.33	1.93	25.34	35.98
T1 + $2H_2O$	−16.46	−17.50	−16.13	−12.40
T3 + $2H_2O$	−15.24	−15.86	−14.35	−7.81
T1 + $(H_2O)_2$	−21.15	−21.79	−12.80	−12.10
T3 + $(H_2O)_2$	−19.93	−20.15	−11.02	−7.51

For the formation of the amine N-chloramine **T1**, N-chlorosuccinimide and **T** collide in a direct manner. While the amine lone pair attacks the chlorine, the proton on the amine is abstracted by oxygen of the carbonyl group of the succinimide

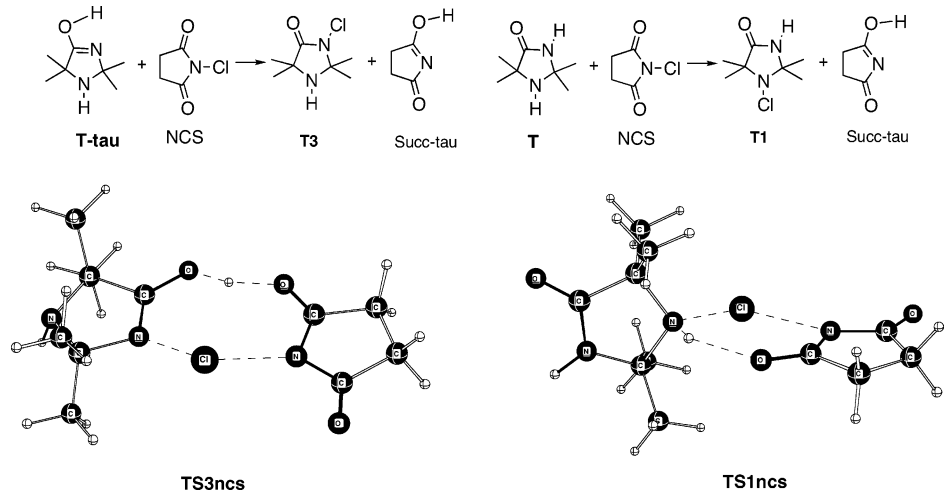


Figure 6. The formation of **T3** and **T1** with NCS.

SCHEME 2: A Proposed Stepwise Mechanism for Chlorine Transfer from T1 to Succinimide

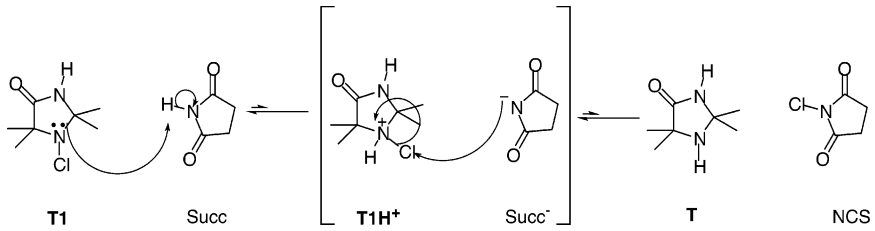


TABLE 6: The Relative Energies, Enthalpies, and Free Energies in kcal/mol at 298 K (Gas Phase, Aqueous Solution, and Chloroform Solution) for the Formation of T1 and T3 from Chlorination of T with NCS

	ΔE	ΔH	ΔG(g)	ΔG(aq)	ΔG($CHCl_3$)
T + NCS	0.00	0.00	0.00	0.00	0.00
T-tau + NCS	12.22	11.90	12.01	15.55	14.00
TS1ncs (**T** + NCS → **T1**)	37.89	38.23	50.18	44.72	46.84
TS3ncs (**T** + NCS → **T3**)	19.03	17.28	30.53	38.77	32.97
T1 + succ-tau	12.51	11.95	12.00	7.86	8.40
T3 + succ-tau	13.74	13.60	13.78	12.45	11.21
T1 + succ	−4.68	−5.09	−4.85	−7.15	−7.52
T3 + succ	−3.45	−3.44	−3.06	−2.55	−4.70

TABLE 7: The Relative Energies, Enthalpies, and Free Energies in kcal/mol at 298 K (Gas Phase, Aqueous Solution, and Chloroform Solution) for Chlorine Transfer from T1 to Succinimide in a Stepwise Mechanism

	ΔE	ΔH	ΔG(g)	ΔG(aq)	ΔG($CHCl_3$)
T1 + succ	0.00	0.00	0.00	0.00	0.00
T1H$^+$ + succ$^-$	131.17	131.16	131.57	35.04	57.15
T + NCS	4.68	5.09	4.85	7.15	7.52

(succ) in a concerted process to yield **T1** and succinimide tautomer (Figure 6). This reaction has a 46.84 kcal/mol free-energy barrier. The enol-tautomer eventually yields the more stable keto form of succinimide.

The formation of **T3** with the NCS method requires tautomerization of **T** to form **T-tau**, which then reacts with NCS. While the lone pair on nitrogen attacks the chlorine on NCS, one of the carbonyl group oxygens of the succinimide abstracts the proton from protonated **T3** to produce the enol form of succinimide, which then rearranges to the keto form of it. This is also a concerted process (Figure 6). Formation of **T3** requires 32.97 kcal/mol from **T-tau**.

In an experimental study,[17] two mechanisms were proposed for the chlorine transfer from **T1** to succinimide. It was postulated that in water, free chlorine in the +1 oxidation state was released. However, it was also mentioned that the chlorine transfer between **T1** and succinimide can occur via "colloidal interaction", since the formation of Cl^+ in a solvent with low polarity such as chloroform is unfavorable. In the former mechanism, it is necessary first to dissociate the **T1** in water, which was found to be not spontaneous in another study.[7] Therefore, for the chlorine to dissociate in water in the presence succinimide, there should be an acid/base reaction first (see Scheme 2). That is, since succinimide is acidic in water, it can donate its proton to the amine nitrogen of **T1**. Then, the succinimide anion (succ$^-$) can attack the positively polarized chlorine to yield **T** and NCS. This mechanism is energetically not favored compared to the concerted mechanism (Table 7).

Experimentally, it was observed that **T3** is formed first, then chlorine is transferred to the amine to form the amine N-

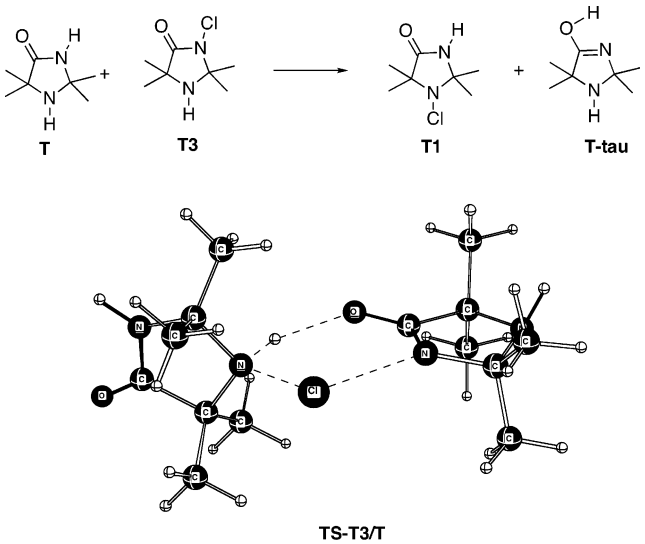


Figure 7. Chlorine transfer from the 3-position to the 1-position with the catalytic action of **T**.

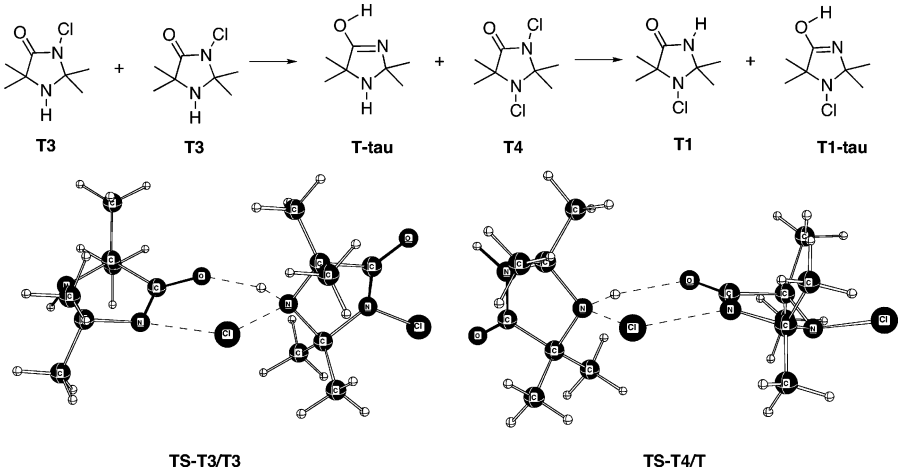


Figure 8. Chlorine transfer from the 3-position to the 1-position via formation of **T** and **T4**.

TABLE 8: The Relative Energies, Enthalpies, and Free Energies in kcal/mol at 298 K (Gas Phase, Aqueous Solution, and Chloroform Solution) for the Chlorine Transfer from the 3-Position to the 1-Position

	ΔE	ΔH	ΔG(g)	ΔG(aq)	ΔG($CHCl_3$)
T3 + T	0.00	0.00	0.00	0.00	0.00
TS−T3/T	45.39	44.99	57.02	59.37	61.90
T1 + T	−1.22	−1.64	−1.78	−4.59	−2.81
T3 + T3	0.00	0.00	0.00	0.00	0.00
TS−T3/T3	47.85	47.35	59.30	66.93	67.68
T-tau + T4	12.70	12.08	11.68	13.79	17.05
T + T4	0.49	0.19	−0.33	−1.76	3.05
TS−T4/T	41.26	40.65	52.53	52.27	57.28
T1-tau + T1	8.59	7.75	7.89	5.85	9.64
T1 + T1	−2.45	−3.29	−3.56	−9.18	−5.62

halamine **T1**. The course of this rearrangement has not been understood to date. In this study, two mechanisms were initially studied for this rearrangement.

In the first proposed mechanism (Figure 7), as soon as **T3** is formed, any **T** can act as a catalyst. Moreover, **T3** acting as a chlorination agent reacts with **T** to yield **T1** and **T-tau** which tautomerizes to the more stable form **T**. **T** is recovered and reacts with additional **T3**. Eventually, all **T3** present should form **T1**. In the second proposed mechanism (Figure 8), upon chlorination, each **T** molecule forms a **T3** molecule. **T3** reacts with another **T3** molecule to form **T4** and **T**. At this point, the question is how much of the **T3** reacts to form **T** and **T4**. If this amount is limited to one molecule, then the reaction would follow the first proposed mechanism. However, if every **T3** forms **T** and **T4**, then **T** and **T4** can react with each other to form two **T1** molecules.

In Table 8, the first proposed mechanism requires 61.90 kcal/mol activation energy. The second proposed two-step mechanism requires 67.68 and 57.28 kcal/mol, respectively.

The two proposed mechanisms for the rearrangement **T3** → **T1** may also be stepwise involving charged species as in the case of chlorination of **T** with NCS. However, the N−Cl bonds on **T1**, **T3**, and **T4** are not as polarized as in the case of NCS. Therefore, any stepwise reaction mechanisms for these cases (**T** + **T3** → **T1** + **T-tau**, **T3** + **T3** → **T-tau** + **T4** → **T1-tau** + **T1**) are not probable under neutral conditions.

When solvation is included for these reactions, it was observed that the activation barrier increased (see Table 8). The reason for this increase in energy is that the transition states are less susceptible to solvation than are the reactants. Even though a rise in energy is observed both in chloroform and water, the outcome of the reactions did not change.

TABLE 9: Relative Energies at 298 K for the Chlorination of T with NCS and a Catalytic Water Molecule

	ΔE	ΔH	ΔG(g)	ΔG($CHCl_3$)
T + NCS + H_2O	0.00	0.00	0.00	0.00[a]
TSncsw1	16.75	14.32	36.96	36.92
T1 + succ-tau + H_2O	12.51	11.95	12.00	8.40[a]
T1 + succ + H_2O	−4.68	−5.09	−4.85	−7.52[a]

[a] Change of state correction (2.40 kcal/mol) not made for bulk water.

It was shown that 1,3-dichloro-5,5-dimethylhydantoin was formed during the rearrangement of chlorine from the 3-position to the 1-position on 5,5-dimethylhydantoin.[9a] In an NMR study, 2,2,5,5,-tetramethylimidazolidin-4-one was chlorinated with 1 equiv NCS.[18] The ^{13}C NMR showed the formation of 1,3-dichloro-2,2,5,5-tetramethylimidazolidin-4-one (**T4**) as an intermediate. With this evidence in mind, the reaction mechanism could proceed through a two-step mechanism involving formation of 1,3-dichloro-2,2,5,5-tetramethylimidazolidin-4-one and 2,2,5,5-tetramethylimidazolidin-4-one, which then react with each other to form 1-chloro-2,2,5,5-tetramethylimidazolidin-4-one.

The other possibility for the chlorine transfer from the 3-position to the 1-position is that the succinimide can act as transfer agent. Although it was observed that forming **T3** is kinetically favored, **T1** is the thermodynamic product. The activation barriers are not as high as in the formation of **T4** and **T** from two molecules of **T3** (the activation barrier for the first step is 67.68 kcal/mol in chloroform) or **T** as chlorine transfer agent from **T3** which has an activation barrier of 61.90 kcal/mol in chloroform. However, if succinimide is acting as a transfer agent, the activation barrier would be 46.84 kcal/mol. This would lead to the conclusion that the transfer of chlorine occurs because the **T1** is the thermodynamic product. Moreover, this activation barrier is lowered by 9.92 kcal/mol by the addition of a catalytic water molecule into the transition state. Therefore, the chlorine migration from position 3 to position 1 is predicted to occur via succinimide as the catalyst.

Three mechanisms have been considered for the disappearance of the initially formed **T3** and the later appearance of **T1** (see Figures 6−8), which have free-energy barriers of 46.84, 61.90, and 57.28 kcal/mol in chloroform at 298 K. These barriers are too high to explain the observed rearrangement which takes place at room temperature. For that reason, we considered a fourth mechanism involving **T**, NCS, and a catalytic water. This lowers the activation barrier by 9.92 kcal/mol. The lower activation barrier indicated that the formation of **T1** was

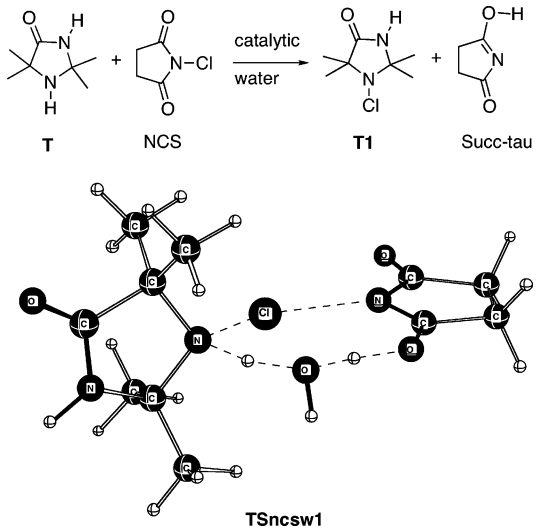


Figure 9. The formation of **T1** with NCS and a catalytic water molecule.

accelerated in the presence of a catalytic water molecule in chloroform (see Table 9 and Figure 9).

Conclusions

In this study, the chlorination mechanism of TMIO was investigated. The hypochlorous acid as a chlorinating agent showed that solvation plays an important role in the reaction energetics. Involving one water molecule into the reaction has both enthalpic and entropic contributions to the free-energy barrier. However, when two waters are participating in the chlorination, as the enthalpic contributions decreased, the entropic contribution increased. Therefore, it is proposed that the reaction mechanism involves two water molecules. The solvation also altered the kinetic and thermodynamic preferences of the reaction outcome. This was related to the **TS1w2** transition state being more polar than the **TS3w2**.

In the chlorination mechanism involving NCS as a chlorinating agent, it was shown that the chlorination of **T** with NCS is in agreement with the experimental results. The solvent effects in these reactions did not change the preferences of the kinetic and thermodynamic products. A stepwise mechanism was also investigated, but it was shown that this mechanism would not be a preferred pathway for the reaction to follow because of the high-energy barriers.

Among the studied mechanisms, formation of **T3** required the tautomerization of **T**. The tautomerization process was investigated for **T** both in water and in chloroform. In water, it was shown that proton transfer can occur via a two- or a one-water bridge. In chloroform, it was shown that a catalytic water contributes to the tautomerization process.

Two possible mechanisms were studied for the rearrangement of chlorine from the 3-position to the 1-position (**T3** → **T1**), and both were calculated to have high free-energy barriers. The chlorination of TMIO (**T**) to **T1** by NCS was found to have a free-energy barrier of 46.84 kcal/mol in chloroform. However, a catalytic water in chloroform is calculated to reduce the free-energy barrier to 36.92 kcal/mol. Thus, we predict that the initial conversion of **T** to **T3** by NCS occurs with a free-energy barrier of 32.97 kcal/mol in chloroform. The subsequent rearrangement to **T1** occurs via **T** (which is in equilibrium with **T3**) via a catalytic water with a free-energy barrier of 36.92 kcal/mol.

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Supporting Information Available: The absolute energies, zero-point energies, enthalpy corrections, entropies and solvation energies tabulated for all related compounds (Table S1); the optimized Cartesian coordinates of all related compounds at the B3LYP/6-311+G(2d,p) level (Table S2); and the ^{13}C NMR spectra of **T**, **T** + NCS mixture (1:1), **T4**, and **T1** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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