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# *N*-Chloro-2,2-dimethyltaurines: a new class of remarkably stable *N*-chlorotaurines

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**Abstract**

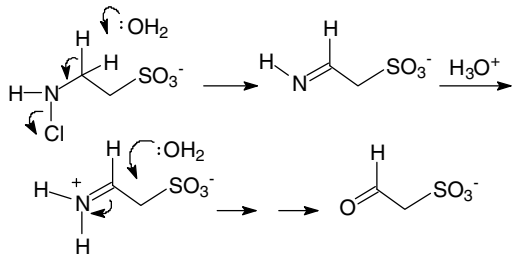
The preparation of novel *N*-chloro-2,2-dimethyltaurine (**4**) and *N*,*N*-dichloro-2,2-dimethyltaurine (**5**) is described. These 2,2-dimethyltaurines were strategically designed to avoid the hydrolytic dehydrochlorination of *N*-chlorotaurines. Thus, they possess long-term stability in contrast to the parent *N*-chlorotaurines, which exhibit broad-spectrum antimicrobial activities.


Activated polymorphonuclear neutrophils (PMNs) play an important role in fighting infection by a process of phagocytosis and destruction of microorganisms. During phagocytosis, they generate reactive oxygen species, such as superoxide anion $O_2^-$ and hydrogen peroxide ($H_2O_2$), and release the contents of the cytoplasmic granules, including myeloperoxidase, into the phagosome.[1,2] Myeloperoxidase catalyzes the oxidation of chloride ions by $H_2O_2$ to produce hypochlorous acid (HOCl),[3,4] a potent oxidizing agent which reacts rapidly with a wide variety of nitrogen-containing compounds to form N–Cl derivatives.[5] Taurine ($NH_2CH_2CH_2SO_3H$) is found in concentrations of 26 and 22 mM in human leukocytes[6] and neutrophils,[7] respectively. It accounts for a large portion of the amines that are available for reaction with HOCl.[8]

*N*-Chlorotaurine (**1**) has been identified as the product of the reaction of HOCl with taurine under physiological conditions.[8,9] Under acidic conditions, or in the presence of excess HOCl, further chlorination of **1** can take place to form *N*,*N*-dichlorotaurine (**2**). Both **1** and **2** have broad-spectrum antimicrobial activities.[10–12] Although **1** is reported to be more stable than other N-chlorinated amino acids,[8] it decomposes slowly to form sulfoacetaldehyde.[13,14] A plausible mechanism for the decomposition of **1** is shown in Scheme 1.

The primary pathway, which leads to the decomposition of these chlorinated amines, is the elimination of HCl to form corresponding imine, which hydrolyzes rapidly to give an aldehyde as the final product. The decomposition of *N*,*N*-dichlorotaurine in solution is believed to proceed through a similar elimination process. This lack of long-term stability limits their use as pharmaceuticals.

To address this issue, it was felt that if the dehydrohalogenation process could be avoided, the *N*-chloramines would be more stable. Toward this end, we chose to prepare the corresponding sodium salts of *N*-chloro- (**4**) and *N*,*N*-dichloro-2,2-dimethyltaurine (**5**) in which both of the




Scheme 1. Proposed mechanism for the decomposition of *N*-chlorotaurine under aqueous conditions.

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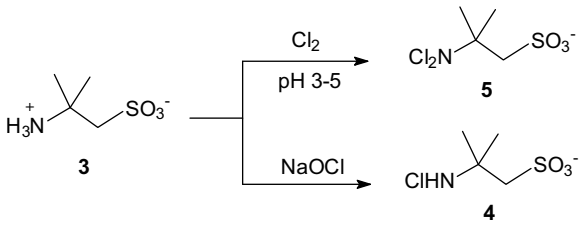
hydrogens on the β-carbon of taurine were substituted for methyl groups.

Prepared through known procedures, 2,2-dimethyltaurine (**3**),[15,16] its chlorination to **4** was carried out in alkaline solution through its reaction with sodium hypochlorite. The synthesis of **5** was accomplished through the chlorination of **3** with chlorine gas in aqueous solution. The pure sodium salt of **5** was isolated as a powder (Scheme 2).[17]

Both **4** and **5** exhibit the characteristic spectra of *N*-chloramines and *N*-dichloramines, respectively (Fig. 1). The molar absorptivities ($\varepsilon$) for *N*,*N*-dichloro-2,2-dimethyltaurine and *N*-chloro-2,2-dimethyltaurine were determined by iodometric titrimetric method. To avoid disproportionation, *N*-chloro-2,2-dimethyltaurine solution was prepared at pH > 8. The measurement gave $\varepsilon_{248\,nm} = 389\ M^{-1}\,cm^{-1}$ for *N*-chloro-2,2-dimethyltaurine **4** and $\varepsilon_{304\,nm} = 297\ M^{-1}\,cm^{-1}$ for *N*,*N*-dichloro-2,2-dimethyltaurine **5**, each measured at their $\lambda_{max.}$ These values for $\lambda_{max}$ and $\varepsilon$ are very similar to those reported for *N*-dichlorotaurine ($\varepsilon_{251\,nm} = 397\ M^{-1}\,cm^{-1}$) and *N*,*N*-dichlorotaurine ($\varepsilon_{302\,nm} = 333\ M^{-1}\,cm^{-1}$).[18]

Solutions of **5** and *N*,*N*-dichlorotaurine were prepared in physiological saline (150 mM NaCl) and their stabilities were examined spectrophotometrically at their $\lambda_{max}$ values. As is shown in Figure 2, **5** is stable over 250 days with no significant decomposition being observable. In contrast, the concentration of *N*,*N*-dichlorotaurine drops 80% in 60 days at room temperature. Moreover, since these solutions were not buffered, the decomposition of *N*,*N*-dichlorotaurine was accompanied by a decrease in pH due to the formation of HCl. From these data, it is clear that the 2,2-dimethyl substitution in **5** results in a dramatic increase in the stability of the *N*,*N*-dichloroamine moiety.




Scheme 2. Chlorination of 2,2-methyltaurine (**3**).

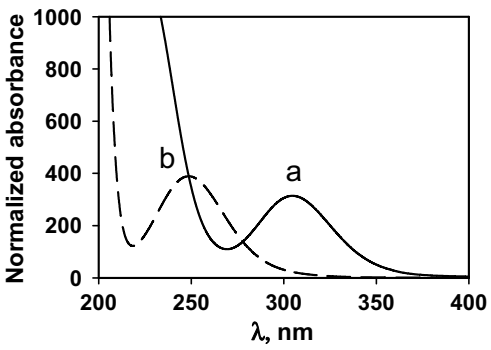



Fig. 1. UV–vis spectra. (a) **5**, $\lambda_{max} = 304$ nm. (b) **4**, $\lambda_{max} = 248$ nm.

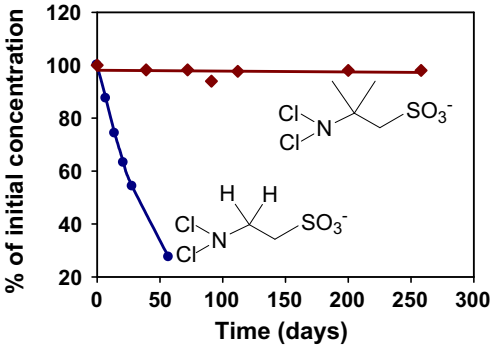



Fig. 2. Stabilities of **5** and **2** at room temperature. Conditions: $[\mathbf{5}]_{initial} = 1.94$ mM, $[\mathbf{2}]_{initial} = 1.47$ mM, initial pH 3.5, 150 mM NaCl, no buffer.

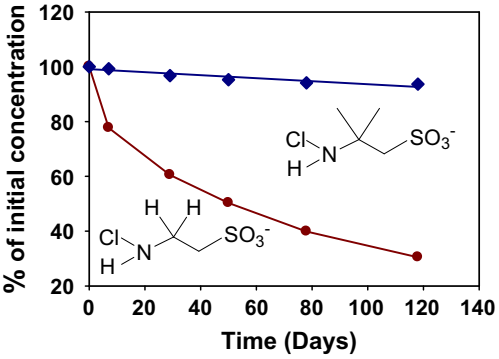



Fig. 3. Stabilities of **4** and **1** at room temperature. Conditions: $[\mathbf{4}]_{initial} = 2.66$ mM, $[\mathbf{1}]_{initial} = 2.50$ mM, initial pH = 7.0–7.2, $[PO_4]_{total} = 4.2$ mM.

To further confirm the above generality, the stability of **4** and *N*-chlorotaurine was compared at room temperature in 4.2 mM phosphate buffered saline at pH 7 (Fig. 3). Clearly, **4** is much more stable than *N*-chlorotaurine. However, **4** is not as stable as **5** under these conditions. It is known that *N*-chloramines disproportionate to form *N*,*N*-dichloramines and the parent amines under acidic or even neutral conditions.[19,20] The reaction rate is faster at lower pH and with increased phosphate concentration. In the present studies, pH 7 was chosen to minimize the disproportionation reaction. The decrease in the concentration of **4** therefore is likely due to the disproportionation process: **4** = **3** + **5**.

In summary, the new *N*-chloro-2,2-dimethyltaurines **4** and **5** have greatly enhanced stability over their *N*-chlorotaurine counterparts. Current studies are underway to establish their antimicrobial properties and suitability for pharmaceutical applications in the treatment of topical infections.

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17. *Typical experimental procedure*: 25 g of 2,2-dimethyltaurine (**3**) was dissolved in 275 mL purified water. Chlorine gas was bubbled into the solution. Chlorine gas reacted rapidly with **3** to produce **5** and HCl. The decrease of pH was controlled by the simultaneous addition of NaOH solution. The pH change was used as an indirect indication of end point. On complete consumption of **3**, the chlorine gas was no longer consumed and the pH drop ceased. Experimentally, this end point determination was sudden and definitive. The solid was isolated by lyophilization. It was then purified by dissolution in 240 mL methanol (anhydrous) and salts (NaCl and $Na_2SO_4$) were filtered out. After the removal of methanol on rotary evaporation under vacum at room temperature, the purified product was isolated in quantitative yield (39 g). Light yellow or off-white solid; $^1$H NMR (400 MHz, $D_2O$): $\delta = 1.56$ (s, 6H), 3.48 (s, 2H). $^{13}$C NMR (50.1 MHz, $D_2O$): $\delta = 23.6$, 56.6, 73.2. Anal. Calcd for $C_4H_8NSO_3Cl_2Na$: C, 19.67; H, 3.28; N, 5.74; S, 13.13; Cl, 29.05; Na, 9.42. Found: C, 19.53; H, 3.13; N, 5.76; S, 13.78; Cl, 29.43; Na, 10.5. MS (ESI) Calcd for $[M-Na]^-$ ($C_4H_8NSO_3Cl_2$) requires $m/z$ ($^{35}$Cl) 220. Found: 220 ($^{35}$Cl, $^{35}$Cl), 222 ($^{35}$Cl, $^{37}$Cl), 224 ($^{37}$Cl, $^{37}$Cl).
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