Bioorganic & Medicinal Chemistry Letters 20 (2010) 3692–3697

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Interaction of heterocyclic thiols/thiones eliminated from cephalosporins with iodine and its biological implications

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ARTICLE INFO

Article history:
Received 2 February 2010
Revised 8 April 2010
Accepted 20 April 2010
Available online 24 April 2010

Keywords:
Antithyroid drugs
Charge-transfer complexes
Iodine
Sulfur compounds
Thiols

ABSTRACT

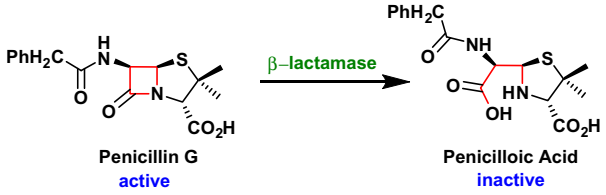
Hydrolysis of β-lactam antibiotics by β-lactamases (e.g., metallo-β-lactamase, mβl) is one of the major bacterial defense systems. These enzymes can catalyze the hydrolysis of a variety of antibiotics including the latest generation of cephalosporins, cephamycins and imipenem. It is shown in this paper that the thiol/thione moieties eliminated from certain cephalosporins by mβl-mediated hydrolysis readily react with molecular iodine to produce ionic compounds having S–I bonds. While the reaction of MTT with iodine produced the corresponding disulfide, MDT and DMETT produced the charge-transfer complexes MDT–I_2 and DMETT–I_2, respectively. Addition of two equivalents of I_2 to MDT produced a novel cationic complex having an almost linear S–I^+–S moiety and I_5^- counter anion. However, this reaction appears to be highly solvent dependent. When the reaction of MDT with I_2 was carried out in water, the reaction produced a monocation having I_5^-, indicating the reactivity of MDT toward I_2 is very similar to that of the most commonly used antithyroid drug methimazole (MMI). In contrast to MMI, MDT and DMETT, the triazine-based compound MTDT acts as a weak donor toward iodine.

Antibiotics based on β-lactams such as penicillins, cephalosporins, penems are the most commonly used drugs for bacterial infections.[1] However, the clinical applications of some of these antibiotics are highly limited due to the production of β-lactamases that inactivate the antibiotics by hydrolyzing the β-lactam ring (Scheme 1). The active site of these enzymes contains either a serine residue (serine-β-lactamases) or zinc ions (metallo-β-lactamases, mβl).[2–7]

Recently, we reported that the heterocyclic thiol side chains present in some of the commonly used antibiotics may possess antithyroid activity.[8] The enzymatic hydrolysis of the β-lactam ring in such antibiotics leads to the formation of thiols, which undergo tautomerism to produce the corresponding thiones. For example, the hydrolysis of cephalosporins having a thio-tetrazole side chain leads to the formation of MTT (**1**) in its thione form (Scheme 2). The thiones produced in the reactions inhibit lactoperoxidase (LPO)-catalyzed iodination reactions, indicating that the hydrolysis of antibiotics having heterocyclic thiol side chains may lead to the generation of antithyroid agents. The efficient and irreversible inhibition of peroxidase-catalyzed iodination by the thiones suggests that the production of β-lactamases and subsequent hydrolysis of antibiotics would affect the thyroid activity.

To further understand the antithyroid activity of heterocyclic side chains in cephalosporins, we have studied the reactivity of heterocyclic thiones toward molecular iodine. It should be noted that the molecular interactions of antithyroid drugs with iodine have been subjected to many investigations because these drugs may inhibit thyroid hormone synthesis by forming donor–acceptor complexes with iodine.[9] Therefore, the identification of products formed in the reactions of the cephalosporin side chains with iodine is crucial in understanding the mechanism of action of these compounds. In this paper, we report, for the first time, that the thiones eliminated from cephalosporins by mβl-mediated hydrolysis readily react with iodine to produce novel donor–acceptor complexes.

Thyroxine (T4), the main secretory product of the thyroid gland, is produced on thyroglobulin by thyroid peroxidase (TPO)/H_2O_2/iodide system. The synthesis of T4 by TPO involves two independent steps: iodination of tyrosine and phenolic coupling of the resulting iodotyrosine residues.[10] The prohormone T4 is then converted to its biologically active form 3,3′,5-triiodothyronine (T3) by a seleno-



Scheme 1. Enzymatic hydrolysis of the β-lactam ring in penicillin G by β-lactamases, leading to the formation of penicilloic acid.

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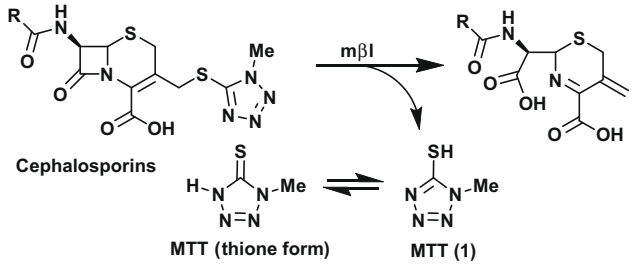
doi:10.1016/j.bmcl.2010.04.087

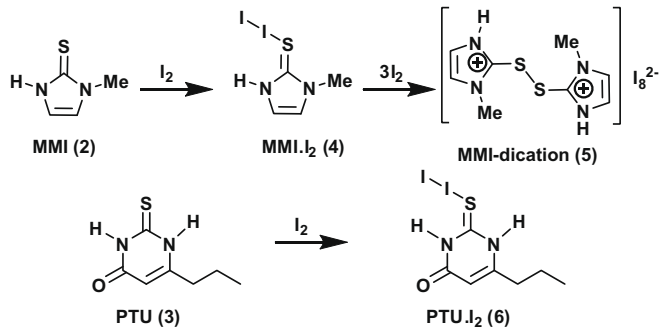


Scheme 2. Elimination of heterocyclic thiol from the hydrolysis of the β-lactam ring in certain cephalosporins by β-lactamases.

cysteine-containing iodothyronine deiodinase (ID-I) enzyme, which is present in highest amounts in liver, kidney, thyroid and pituitary.[11] The 5′-deiodination catalyzed by ID-I is a ping-pong, bisubstrate reaction in which the selenol (or selenolate) group of the enzyme (E-SeH or E-Se−) first reacts with T4 to form a selenenyl iodide (E-SeI) intermediate. Subsequent reaction of the selenenyl iodide with an as yet unidentified intracellular cofactor (1,4-dithiothreitol, DTT, in vitro) completes the catalytic cycle and regenerates the selenol.[11,12] Therefore, the iodination and deiodination reactions involving various forms of iodine is essential for the metabolism of thyroid hormones.

However, an overproduction of T4 and T3 lead to hyperthyroidism, which can be treated by antithyroid drugs such as methimazole (**2**, MMI) and 6-*n*-propyl-2-thiouracil (**3**, PTU). It has been proposed that MMI and PTU may divert oxidized iodides away from thyroglobulin by forming stable electron donor–acceptor complexes with iodine, which can effectively reduce the thyroid hormone biosynthesis.[13] Interestingly, all the thione-based antithyroid drugs known to-date have been shown to form donor–acceptor complexes with iodine.[14–16] Isaia et al. have shown that MMI reacts with I_2 to form a stable MMI–I_2 charge-transfer adduct (**4**) or a dicationic disulfide (**5**) species depending upon the concentration of iodine and the nature of reaction medium.[14a,16] The reaction of PTU with iodine produces exclusively the PTU–I_2 charge-transfer complex (**6**),[17] although the sulfur–iodine interactions in the PTU–I_2 complex (**6**) are slightly weaker than that of MMI–I_2 adduct (Scheme 3).

As previously mentioned, the mβl-mediated hydrolysis of cephalosporins such as cefamandole, moxalactam, cefazolin, cefmetazole, cefoperazone and ceftriaxone eliminates the thiol side chains, which undergo a rapid tautomerism to produce the corresponding thiones (Fig. 1).[8] Based on the effect of these thiones on peroxidase-catalyzed iodination reactions, it has been proposed that the antithyroid activity of heterocyclic side chains must be taken into account while designing new antibiotics based on cephalosporins. Furthermore, it is known that the thiones capable of forming



Scheme 3. Interactions of the commonly used antithyroid drugs methimazole (MMI) and 6-*n*-propyl-2-thiouracil (PTU) with iodine.

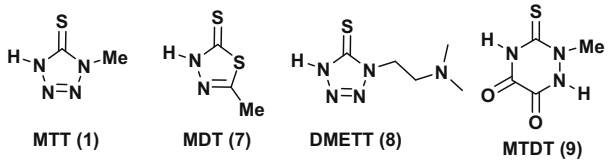


Figure 1. Structures of some heterocyclic thiones eliminated from cephalosporin antibiotics such as cefamandole, moxalactam, cefazolin, cefmetazole, cefoperazone and ceftriaxone.[8]

strong donor–acceptor (D–A) complexes are better antithyroid agents than that produce weak D–A complexes.[14a] Therefore, it was considered to be of interest to compare the reactivity of MTT, MDT, DMETT and MTDT to that of MMI and PTU toward molecular iodine.

Addition of iodine to MTT produced the corresponding disulfide·I_2 (MTTox·I_2, Fig. S6 Supplementary data) as the major product. The X-ray crystal structure[18] indicates that the compound has crystallized in a C2/*c* space group of monoclinic system and the unit cell contains some iodine molecules. Our attempts to isolate the MTT–I_2 charge-transfer complex were unsuccessful. This is probably due to the facile oxidation of MTT to the corresponding disulfide in the presence of iodine. As MMI is more zwitterionic than MTT, the nature of C=S bonds may be responsible for the differences in the reactivity of these two compounds towards iodine. However, the FT-Raman spectrum shows the formation of the expected compound. On the other hand, when MDT was treated with one equivalent of iodine, the reaction produced the corresponding charge-transfer complex MDT–I_2 (**10**). The crystal structure of MDT–I_2 indicates that the S–I–I moiety adopts a linear arrangement (Fig. 2). The I(1)–I(2) bond length of 2.8806(17) is considerably elongated with respect to the I–I bond length in crystalline iodine (2.715 Å, at −163.1 °C).[19] As a result, the C–S bond (1.702(7) Å) is also elongated, indicating a reduced C–S double-bond character.

The reaction of DMETT (**8**) with iodine produced the sulfur–iodine adduct **11** (Fig. 2) having anionic thiolate moiety. In contrast to I_2 adducts of organic sulfides, $R_2S\cdots I_2$, and thiones, $R_2C{=}S\cdots I_2$, the formation of thiolate–iodine charge-transfer adduct is unprecedented in heterocyclic thiolate chemistry because the reactions of thiolates with iodine generally produce the corresponding disulfides. Darensbourg and co-workers have shown that a mononuclear nickel thiolate having sterically hindered substituents forms 1:1 thiolate–iodine charge-transfer adduct.[20] However, in this particular case, the thiolate coordination to nickel is intact in the thiolate–iodine complex and the sulfur interacts with iodine through its lone pair with tetrahedral character. In the DMETT·I_2 complex (**11**), the completely anionic thiolato sulfur interacts with I_2 leading to formation of an almost linear arrangement of S–I–I bonds (173.6°). The S(1)–I(1) bond length of 2.545 Å indicates that the S–I bond in this complex is significantly stronger than that of MMI·I_2 (**4**), MDT·I_2 (**10**) and other related iodine adducts derived from thiones (Table 1). This strong interaction leads to an I–I bond length of 3.0310(5) Å, which is significantly longer than that of free iodine in gaseous state (2.667(2) Å), and in the solid state (2.715(6) Å). Although DMETT (**8**) exists predominantly in its thione form as shown by theoretical calculations,[21] the coordination of sulfur to iodine increases the acidity of N–H proton that can be abstracted intermolecularly by the $-NMe_2$ group (Scheme 4). As a consequence, the electron density around the C=S bonds moves towards S–I–I bond, which leads to an elongation of the I–I bond.

In the reaction between **10** and I_2 in dichloromethane, the concentrations of I_2 appear to change the nature of products. Interestingly, addition of two equivalents of I_2 to MDT produced a novel cationic complex (**12**) having an almost linear S–I^+–S moiety and I_5^- counter anion (Fig. 3a). The strong inhibitory activity of MDT

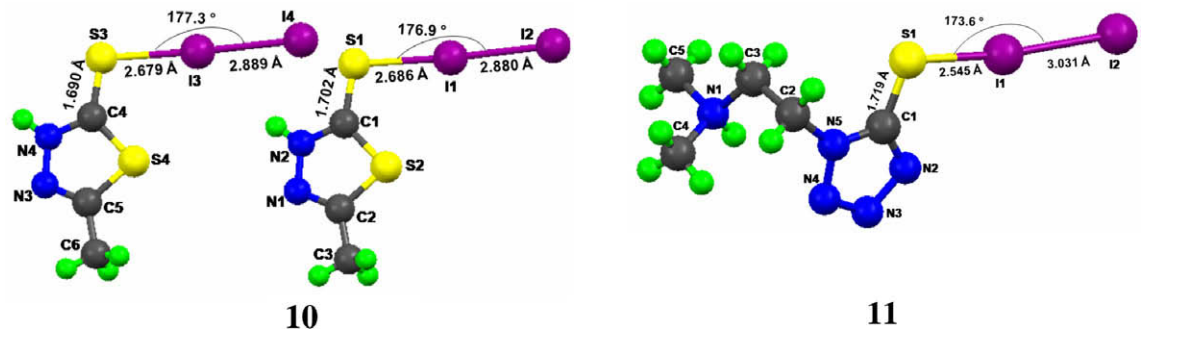
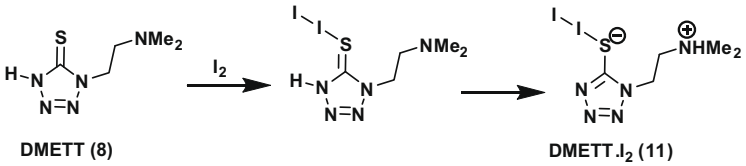


Figure 2. X-ray crystal structures of MDT·I_2 (**10**) and DMETT·I_2 (**11**) charge-transfer complexes showing some important bond lengths and angles.

Table 1
A comparison of C–S, S–I and I–I bond lengths, charges on S and I atoms and I–I bond orders between the charge-transfer complexes obtained from various thiones.

Compound	Bond length (Å)[a]			$\nu_{(I-I)}$[b]	Charge[c]			(I–I) Bond order[d]
	C–S	S–I(1)	I(1)–I(2)		q_S	$q_{I(1)}$	$q_{I(2)}$	
MMI·I_2 (**4**)	1.725(3)	2.593(1)	2.9912(2)	141	−0.116	−0.045	−0.345	0.53
PTU–I_2 (**6**)	1.696(4)	2.7805(10)	2.8264(4)	150	−0.118	−0.046	−0.188	0.77
MDT·I_2 (**10**)	1.702(7)	2.686(2)	2.8806(17)	121	0.001	−0.042	−0.266	0.64
DMETT·I_2 (**11**)	1.719(5)	2.5454(16)	3.0310(5)	104	−0.162	0.008	−0.426	0.44
MTDT–I_2 (**15**)	1.683(3)	3.1298(17)	2.7616(13)	170	−0.195	−0.039	−0.107	0.95

[a] The bond lengths were taken from crystal structures.
[b] FT-Raman spectrum in the $\nu_{(I-I)}$ region.
[c] The natural charges were obtained from NBO calculations at B3LYP level by using 6-311G* basis set for C, H, N and S and LANL2DZ-ECP basis set for iodine.
[d] The bond order of I–I (n) calculated according to Pauling's equation $d = d_0 - c \log n$, where $d_0 = 2.715$ Å and $c = 0.85$ Å.



Scheme 4. Reaction of thione **8** with I_2 to produce the zwitterionic DMETT·I_2 complex (**11**) by intermolecular proton transfer.

in the LPO-catalyzed iodination and formation of the unusual [{MDT_2I^+}I_5^-] complex led us to further study the nature of S–I and I–I interactions in complex **12**. It has been shown that I_5^- can be considered as a mixture of I_3^- and I_2 or I^- and $2I_2$. The X-ray crystal structure of complex **12** shows that the bond lengths of I(6)–I(5) and I(6)–I(2) are much longer than that of I(2)–I(3) and I(4)–I(5). Therefore, the I_5^- anion in complex **12** can be described as I^- and $2I_2$ rather than an I_3^- and I_2 mixture. This is further supported by the FT-Raman spectrum, which exhibited two strong bands at 168 and 139 cm^{-1} for the symmetric stretching of two I–I bonds in complex **12** (Fig. 3c). These observations indicate that the addition of excess iodine to MDT·I_2 complex produces I^- ions by a heterolytic cleavage of the I–I bond and each I^- ion produced in the reaction forms complex with two iodine molecules to generate the unexpected [{MDT_2I^+}I_5^-] species. This is formed via the formation of compound **13** (Fig. 3b). The weak interaction of the MDT·I_2 with the I_2 of the other unit indicates that during the slow addition of iodine, the MDT in solution can attack the S–I^+ and can form the cationic complex S–I^+–S moiety, as shown in Scheme 5. The rapid addition of iodine in dichloromethane leads to the formation of compound **13**. The S–I and I–I bond lengths in **13** are intermediate between compounds **10** and **12**, indicating that the conversion of **10**–**12** proceeds via the formation of intermediate **13**. These observations are further supported by the FT-Raman spectrum of compounds **13** (Fig. 3d) and **12** (Fig. 3c).

Similar to the effect of I_2 concentration, the choice of solvent has a large influence on the nature of products formed. When MDT was treated with I_2 in water, the reaction produced the monocation **14** containing a disulfide bond as the major product. The X-ray crystal structure of **14** (Fig. 4a) shows that the monocations in the compound are stabilized by I_5^- ions. The formation of **14** is interesting from a chemical point of view, as only one of the thiadiazole rings undergoes oxidation. The bond lengths between the iodine atoms and the FT-Raman spectrum of **14** indicate that by the I_5^- counterion can be considered as $2I_2 \cdot I^-$ adduct. Compound **14** represents a rare example of monocation having an S–S bond. The formation of such species has been previously reported for MMI, which reacts with I_2 in water to produce a monocation containing an S–S bond and I_3^- and I_5^- as counterions. In dichloromethane, however, MMI afforded a dication disulfide containing I_8^{2-} as counterion.[14a] Based on these observations, it has been proposed that the dication and monocation disulfides might be effective intermediates in the reaction of MMI with an active iodine species depending on the pH and I_2 concentration in the thyroid gland.[14a] The high reactivity of MDT toward I_2 and the relatively low IC_{50} value in the LPO-catalyzed iodination reaction,[8] suggest that MDT should have strong antithyroid activity.

In contrast to MMI, MDT and DMETT, the triazine-based compound MTDT acts as a weak donor towards iodine (Fig. 5). The S–I length in MTDT·I_2 (**15**) (3.129(17) Å) is much longer than that

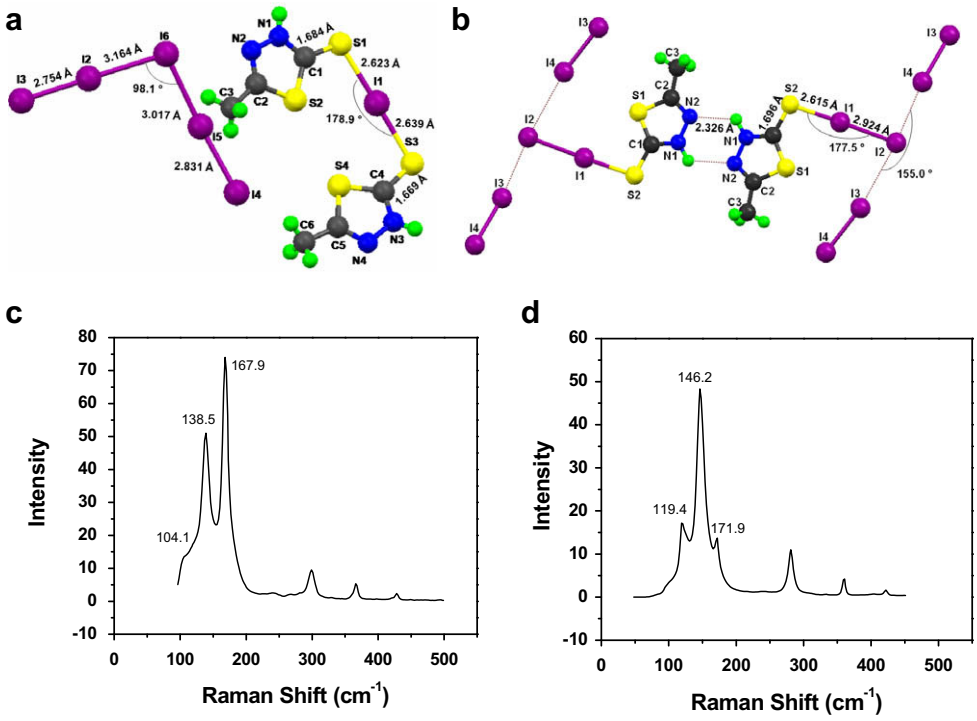
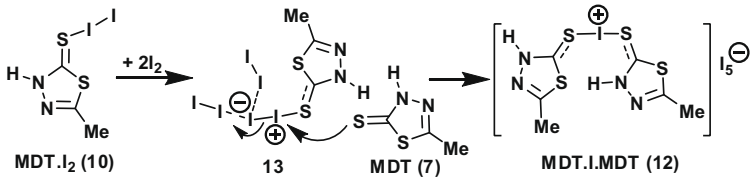


Figure 3. (a) X-ray crystal structure of complex (**12**), exhibiting a linear S–I^{+}–S moiety. (b) MDT·I_2·I_2 (**13**) showing the weak interaction with the iodine of other unit (c) FT-Raman spectra of complex **12** showing two strong bands at 139 and 168 cm^{-1} for I_5^-. (d) FT-Raman spectra of complex **13** showing the weak interaction of MDT·I_2 (119 cm^{-1}) with molecular iodine (172 cm^{-1}).



Scheme 5. The proposed mechanism for the formation of [MDT–I–MDT]I_5 via intermolecular reaction between complex **10** and MDT in the presence of an excess amount of iodine.

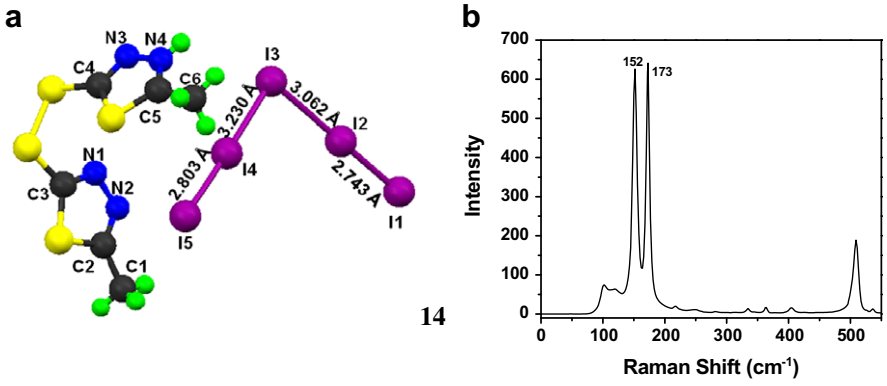


Figure 4. (a) The crystal structure of **14** [MDTox–H]I_5 obtained by the reaction of MDT and I_2 in water. (b) The FT-Raman spectra of the complex [MDTox–H]I_5.

of PTU·I_2 (2.7805(10) Å) and other imidazole/triazole-based compounds (Table 1). Furthermore, one of the two ketonic groups in the heterocyclic ring exists in its enol form. This allows the formation of a hydrogen bonding network between two MTDT·I_2 molecules mediated by water coordination. The I–I bond order calculated for MTDT·I_2 (0.95) also indicates that the S···I interaction is much weaker than that of PTU·I_2.[17] Although MTDT is an efficient inhibitor of LPO-catalyzed iodination,[8] this compound is a very poor scavenger of iodine as compared to PTU. These observations suggest that MTDT should exhibit its antithyroid activity mainly by inhibiting the peroxidase-catalyzed iodination reactions.

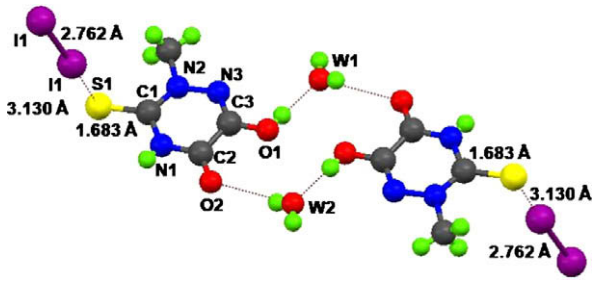


Figure 5. X-ray crystal structure of MTDT·I_2 complex (**15**) showing a hydrogen bonding network via water molecules.

Based on the I–I bond lengths and bond orders (Table 1), the D–I_2 adducts (i.e. MMI·I_2 (**4**), MDT·I_2 (**10**), DMETT·I_2 (**11**), MTDT·I_2 (**15**) and PTU·I_2 (**6**) complexes) can be classified into three structural types (D···I_2, D–I–I, [(D–I)$^+$···I^-]).[22] The iodine complexes of MTDT and PTU belong to the first category (D···I_2) in which the donor–acceptor (D–A) interactions are weak and the I–I bond lengths are comparable to that of free iodine in the solid state (2.715(6) Å). MDT·I_2 (**10**) can be considered as a D–I–I adduct, which is similar to the iodine adducts of compounds having more thione (C=S) character. The DMETT·I_2 complex (**11**) should be described as (D–I)$^+$···I^- adduct in which the I–I bond is almost dissociated into an ion pair. Although the classification of DMETT·I_2 (**11**) is similar to the one proposed previously for MMI·I_2 adduct,[16] the I–I bond order in DMETT·I_2 (**11**) (0.44) is considerably lower than that of MMI·I_2 (0.53), indicating that the donor ability of DMETT (**8**) toward iodine is significantly higher than that of MMI (**2**). The FT-Raman spectra also confirm the stronger interaction in compound **11** as compared to other similar donor–acceptor adducts (Fig. S2).

A plot of I–I frequencies obtained from the Raman spectra versus I–I bond orders shows a linear line, indicating an excellent correlation between these two parameters (Fig. 6). The I–I bond order and Raman shift for MTDT–I_2 (**15**) is almost close to that of free iodine. This suggests that the triazine-based thione **9** is a very poor donor toward molecular iodine. Furthermore, MTDT–I_2 is much weaker than PTU·I_2 complex (**6**), suggesting that the antithyroid activity of MTDT should be lower than that of PTU. On the other hand, the nature of sulfur–iodine interactions in the tetrazole and thiadiazole-based compounds **10** and **11** is almost identical to that of MMI·I_2 (**4**). This indicates that the antithyroid activity of MDT (**7**) and DMETT (**8**) is expected to be similar to that of MMI (**2**). In agreement with this, the activity of MTDT on LPO-catalyzed iodination was found to be lower than that of PTU and MMI. MDT and DMETT, on the other hand, exhibited much higher activity as compared to PTU and MTDT.[8] These observations suggest that the side chains of antibiotics (thiones) that exhibit strong peroxidase inhibition are likely to form strong donor–acceptor complexes with iodine.

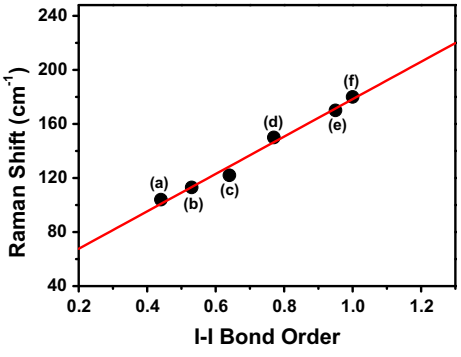


Figure 6. The plot of I–I bond order versus Raman shift for the charge-transfer complexes of various thiones with molecular iodine. (a) DMETT·I_2 (**11**), (b) MMI·I_2 (**4**), (c) MDT·I_2 (**10**), (d) PTU–I_2 (**6**), (e) MTDT–I_2 (**15**), (f) free iodine.

In conclusion, this study provides the first experimental evidence that the heterocyclic side chains present in cephalosporins not only effectively inhibits the peroxidase-catalyzed iodination reactions, but also reacts with I_2 to produce novel charge-transfer complexes. These observations indicate that the chemical reactivity of the side chains (thiones) present in cephalosporins is very similar to that of the commonly used antithyroid drugs. The thiones having high inhibitory potency toward peroxidase-catalyzed reactions appear to form strong donor–acceptor complexes with iodine. These studies suggest that the effect of heterocyclic side chains on peroxidases and the reactivity of these compounds toward iodine must be taken into account while designing new antibiotics based on cephalosporins as the combined effect of these side chains upon elimination may adversely affect the thyroid activity.

Acknowledgments

This study was supported by the Department of Science and Technology (DST), New Delhi, India. G.M. acknowledges the DST for the award of Ramanna and Swarnajayanti fellowships and A.T. thanks the University Grants Commission (UGC) for a research fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.087.

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