Check for updates

View Article Online
View Journal

ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: G. Roy, R. Karri, R. Das, R. K. Rai and A. Gopalakrishnan, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC02232B.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Please do not adjust margins

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/D0CC02232B

Journal Name

COMMUNICATION

Hg–C Bond Protonolysis by A Functional Model of Bacterial Enzyme Organomercurial Lyase MerB

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Ramesh Karri,† Ranajit Das,† Rakesh Kumar Rai,† Anaswara Gopalakrishnan,† Gouriprasanna Roy*‡

Published on 20 May 2020. Downloaded by National University of Singapore on 5/24/2020 8:24:52 AM.

Herein, we report a novel synthetic compound **1**, having a highly nucleophilic selenolate (Se^-) moiety and a thiol (-SH) functional group, which showed efficient Hg–C bond protonolysis of various R–Hg–X molecules including neurotoxic methylmercury and thimerosal, via direct -SH proton transfer to highly activated C-atom of departed R group with low activation energy barrier at room temperature (21 °C), in the absence of any external proton source and, thus, acts as a functional model of MerB.

Methylmercury ($MeHg^+$) is a ubiquitous environmental pollutant and a potent neurotoxin.[1] It accumulates at high levels in food chains, mainly in fish and seafood, and therefore, consumption of these contaminated foods poses a significant risk to human health.[2] On the other hand, exposure to ethylmercury ($EtHg^+$) is an another serious concern in developing countries where $EtHg^+$-containing antimicrobial agent "thimerosal" is commonly used as a preservative in multiuse vials of vaccines and in other medicines.[2,3] In nature, mercury-resistant bacteria having *mer* operon detoxify a wide variety of $R–Hg^+$ (R = alkyl or aryl) with the help of a series of *mer* proteins including organomercurial lyase MerB that catalyzes the protolytic Hg–C bond cleavage and produces Hg^{2+} and RH (Fig. 1a).[4]

The active site of MerB consists of a catalytic triad of two cysteine residues (Cys-96 and Cys-159, numbering of the *E. coli* MerB sequence, plasmid R831b) that are strictly conserved in all known variants of MerB and either an aspartic acid, Asp-99, residue (present in most known variants of MerB) or a serine (Ser) residue (present in few MerB variants).[5,6] Early studies suggest that the deprotonation of Cys-96 by Asp99 possibly initiates the nucleophilic attack of Cys-96 on substrate RHgSR'. The subsequent attack by Cys-159 displaces exogenous thiol R'SH and forms tri-coordinated Hg species (mechanism–I).[5-9] In this model, Asp-99 serves as a proton mediator for Hg–R protonolysis.[5,10] In an alternative model, the Cys-159 attacks on RHgSR' and the second cysteine Cys-96 almost simultaneously coordinates to the Hg center with concomitant transfer of SH proton directly to the leaving R group (mechanism–II).[11] On contrary, a very recent study by Omichinski and co-workers revealed that the initial binding of organotin and organolead to MerB occurs through Asp-99 followed by binding to Cys-96 and Cys-159.[12]

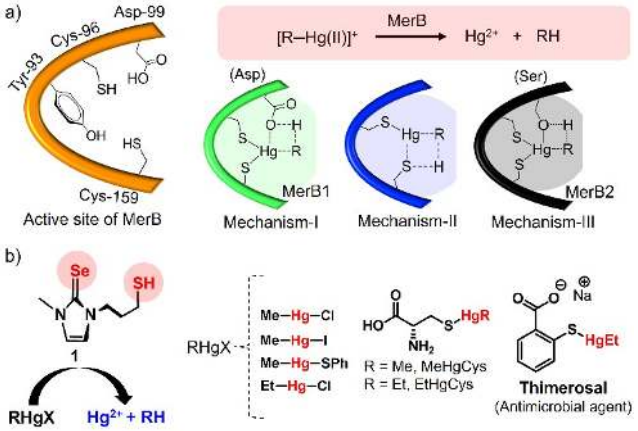


Fig. 1 (a) Active site of MerB and proposed mechanisms for Hg–C protonolysis of organomercurials catalyzed by MerB variants.[9] (b) The Hg–C bond protonolysis of various organomercurials including thimerosal by **1** at 21 °C.

Studies with various MerB proteins (they differ in protein sequence)[13] revealed that the reactivity and the substrate specificity of all MerB proteins are not similar. The MerB protein, derived from *Bacillus megaterium* with a serine residue at the active site, referred as *B. megaterium* MerB2 protein, shows much lower Hg–C bond cleavage activity in comparison to *B. megaterium* MerB1 protein with an aspartic acid residue at the active site.[6,14] However, the mechanism by which serine-containing MerB2 proteins catalyze the Hg–C protonolysis is not clear yet.

Nevertheless, all MerB variants uses two cysteine residues for Hg–C protonolysis–one thiolate (S^-) group for the activation of otherwise inert Hg–R bond and one thiol (SH) group for the activation as well as the transfer of thiol proton to the activated R group, either directly or via a mediator.[5,10] A few prominent synthetic research groups,[15,17,18] over the last few decades, have focused to emulate the function of MerB using tridentate ligands (L_3), having either three phosphorous or sulfur donor centers (Fig. S1 in ESI†), to afford a higher coordinated mercury alkyls of type $R\text{-}Hg(L)_3$ for the activation of Hg–R bond.[8,9] However, in all previous models, an external proton donor, either Brønsted acid[15,17] or excess thiol[15,18] was used for Hg–C bond protonolysis. A great challenge, therefore,

† *Department of Chemistry, School of Natural Sciences, Shiv Nadar University, NH91, Dadri, Gautam Buddha Nagar, UP 201314, India.*
‡ *Department of Chemistry, Indian Institute of Technology Tirupati, Tirupati, A.P. - 517506, India. E-mail: gproy@iittp.ac.in*
†Electronic Supplementary Information (ESI) available: [Synthetic details, NMR spectra and details of DFT calculations. See DOI:

ChemComm Accepted Manuscript

Please do not adjust margins

Published on 20 May 2020. Downloaded by National University of Singapore on 5/24/2020 8:24:52 AM.

is to design a molecule which can play dual role, i.e., the activation of Hg–R bond and simultaneously or concurrently donation of proton to the activated R group, either directly or via a mediator. In addition, as the nature of Hg–C bond of two coordinated $MeHg^+$ species Me–Hg–X is critically dependent upon the type of $MeHg^+$-binding ligand X,[19,20] it is, therefore, essential to develop a synthetic molecule which can facilitate the protolytic Hg–C bond cleavage of a wide variety of environmentally and biologically relevant organomercurials (Fig. 1b). Herein, we report a simple imidazole-based selone **1**, having an –$N(CH_2)_3SH$ substituent, which showed remarkable ability to protolytically cleave the Hg–C bonds of various organomercurials (R–Hg–X) under mild conditions *via* direct proton transfer to the activated R group, in the absence of any external proton donor.

To our surprise, the addition of **1** (25 mM) to a solution of EtHgCl, at a 1:1 molar ratio, led to a gradual decrease of ethyl (–HgEt) peak in ^1H NMR spectroscopy with concomitant formation of ethane (C_2H_6) gas, which was observed at 0.82 ppm in DMSO-d_6[21a] (Figs. 3a, S2-S6). All NMR experiments were performed in sealed NMR tubes at 21 °C. Likewise, the evolution of methane (CH_4) gas was observed at 0.2 ppm in DMSO-d_6)[21b] in the reactions of MeHgX (25 mM, X = SPh, Cl or I) and **1**, in 1:1 molar ratio at 21 °C (Fig. 3b). The gradual increase of dissolved CH_4 or C_2H_6 in DMSO-d_6 (in a sealed NMR tube) was observed over time which disappeared in open air (Figs. 3c and 3d). Similarly, the cleaved product benzoic acid was detected by LC/MS when 4-Chloromercuribenzoic acid was treated with 1 equiv of **1** (Fig. S29). Detailed kinetic studies revealed that the Hg–C bond cleavage of EtHgCl by **1** occurred at a faster rate than the Hg–C bond cleavage of MeHgI or MeHgCl. The initial rates of Hg–C bond protonolysis of RHgX are in the order of EtHgCl > MeHgI >> MeHgCl under identical conditions at 21 °C, indicating that the Hg–C bond in MeHgCl is relatively inert in nature compared to the Hg–C bonds in EtHgCl and MeHgI. It is pertinent to mention here that the Hg–C bond protonolysis occurs slowly at the initial stage of the reaction. This is mostly due to the time require to form 1:1 adduct followed by the activation of the Hg–C bond (*vide infra*). This induction time is more in case of MeHgCl than MeHgI or EtHgCl.

To investigate the role of Se center in **1** on Hg–C bond cleavage we have employed **2** and a benzimidazole-based compound **3** in our study (Fig. 2). A slow protolytic Hg–C bond cleavage of MeHgI, either by **2** or **3**, was observed under identical reaction conditions (Table 1, Figs. S7-S10). The rate of protonolysis by these selones is in the order of **1** > **2** > **3**. The Natural Population Analysis (NPA)[10a,22] of optimized structures revealed that these selones exist in zwitterionic form with large negative charge on the Se center and the delocalized positive charge in the ring (Fig. 2b and Scheme S5).[23] Interestingly, the amount of negative charge on Se center of these selones is in the same order of their reactivity, **1** (-0.469) > **2** (-0.456) > **3** (-0.409), (Table S3). Moreover, HOMO/LUMO analysis confirmed that the energy gap between the HOMO of **1** (donor) and the LUMO of MeHgI (acceptor) is the lowest and, hence, the most reactive among these three selones (Fig. S37).

^1H resonance of Me group of $MeHg^+$ (NMR study) in the presence of a chelating ligand provides very useful information on the extent of Hg–C bond activation by ligand. Detailed ^1H resonance study clearly showed that **1** ($\Delta\delta$ = 0.168 ppm) exerted large upfield shift of Me resonance of MeHgI compared to other selones such as **2** ($\Delta\delta$ = 0.157 ppm), **3** ($\Delta\delta$ = 0.154 ppm), and **4** ($\Delta\delta$ = 0.06 ppm), (see details in ESI†, Fig. S13). Moreover, the ^{199}Hg NMR of a 1:1 solution of **1** / MeHgI (0.1 M) showed a resonance at -850 ppm (^{199}Hg of MeHgI appeared at -1153 ppm, $\Delta\delta$ = 303 ppm), suggesting that **1** interacts strongly to the Hg center of MeHgI (Fig. S13c). In fact, the X-ray structures of a 1:1 adduct of MeHgI and **1** and **5** confirmed that the Se center of imidazole-based selone **4** interacts more strongly with the Hg center of MeHgI ($d_{Hg\text{-}Se}$ = 2.494Å) than the Se center of benzimidazole-based selone **5** ($d_{Hg\text{-}Se}$ = 3.077Å), (Figs 4a and 4b).

View Article Online

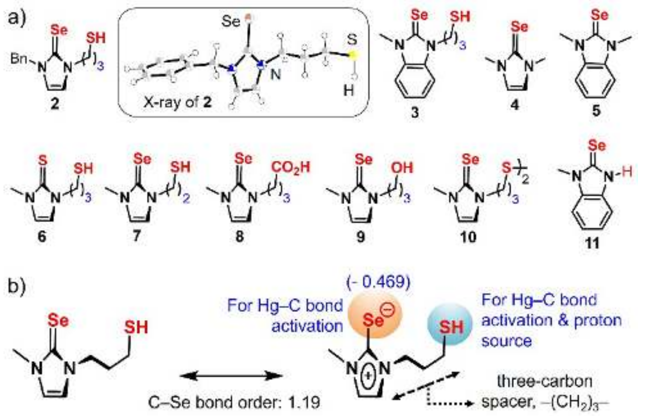


Fig. 2 (a) Structures of various selones and X-ray of **2**. (b) Zwitterionic resonance structures of **1** showing atomic partial charge on Se center (calculated).

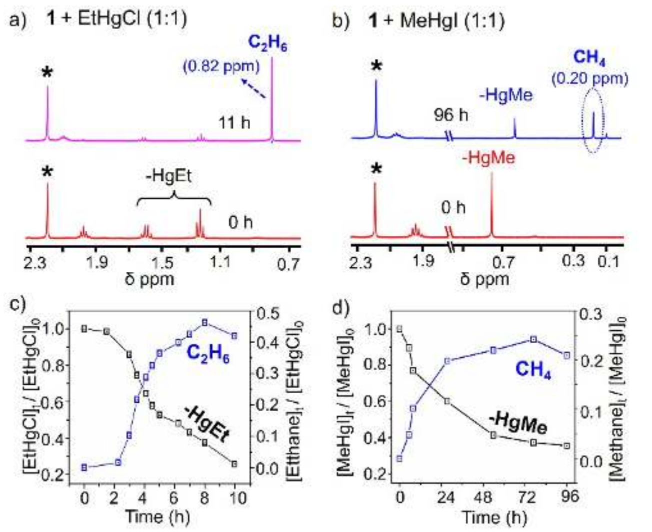


Fig. 3 ^1H NMR spectra of a 1:1 solution of **1** / EtHgCl (25 mM) (a), **1** / MeHgI (25 mM) (b), showing only –HgEt and –HgMe peaks and formation of the corresponding C_2H_6 and CH_4, respectively (* = external standard, mesitylene; recorded in DMSO-d_6 at 21 °C). Graphs showing the degradation of EtHgCl (c) and MeHgI (d) by **1** and formation of the dissolved C_2H_6 and CH_4, respectively, at 21 °C.

Table 1 Initial rates of Hg–C protonolysis by various selones at 21 °C.

SR NO.	Compd.	RHgX	Initial Rate ($M.h^{-1}$)[a]
1	**1**	EtHgCl	7.38 ± 0.5 x 10^{-3}
		MeHgI	4.21 ± 0.2 x 10^{-3}
		MeHgCl	0.07 ± 0.5 x 10^{-3}
2	**2**	MeHgI	1.96 ± 0.2 x 10^{-3}
3	**3**	MeHgI	0.98 ± 0.12 x 10^{-3}
4	**7**	MeHgI	1.31 ± 0.12 x 10^{-3}
5[b]	**6**	MeHgI	1.78 ± 0.14 x 10^{-3}
6	**1**	Thimerosal	2.07 ± 0.2 x 10^{-3}
		EtHgCys	1.2 ± 0.3 x 10^{-3}
		MeHgCys	0.4 ± 0.02 x 10^{-3}
		MeHgSPh	0.16 ± 0.14 x 10^{-3}

[a]All experiments were carried out in a sealed NMR tube in DMSO-d_6 at 21 °C; [RHgX] = [Compd.] = 25 mM; [b][**6**] = [MeHgI] = 100 mM.

Interestingly, when Se atom was replaced with S atom in **1**, the protonolysis reaction by **6** (25 mM) occurred very slowly—no Hg–C bond cleavage was observed even after 4 days at 21 °C. However, at

ChemComm Accepted Manuscript

Please do not adjust margins
View Article Online

Published on 20 May 2020. Downloaded by National University of Singapore on 5/24/2020 8:24:52 AM.

higher concentration (100 mM) we did observe the slow disappearance of Me (of MeHgI) or Et (of EtHgCl) peak in NMR spectroscopy with the appearance of CH_4 or C_2H_6 gas, (Fig. S12). Moreover, the rate of Hg–C bond cleavage by **1** is ~3 times higher than the rate obtained by **7**, indicating that the three-carbon spacer, $–(CH_2)_3–$ in $–N(CH_2)_3SH$, is likely assisting -SH group to locate close to the –HgR group for facile Hg–C protonolysis.

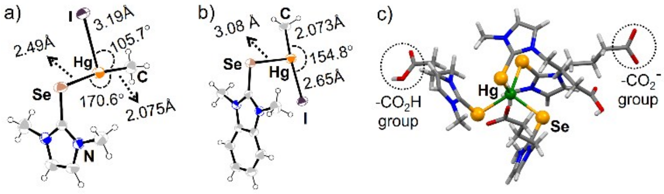


Fig. 4 X-ray structures of **4**.MeHgI (a), **5**.MeHgI (b), and **12** (c).

In general, the pK_a value of acid group (–COOH) is lower in comparison to the hydroxyl group (-OH) and, thus, the acidic group of **8** is expected to donate a proton to the activated C-atom, similar to **1**. However, to our disappointment, in the reaction of **8** and MeHgI we observed highly toxic Me_2Hg formation via a 4-membered cyclic intermediate (Fig. S15),[24] instead of CH_4. Addition of excess amount of **8** to the above reaction led to the formation of a tetra-selenium coordinated mononuclear neutral Hg complex **12** (Fig. 4c), which confirms that the carboxylic group (hard base) is located far away from the Hg center (soft acid) and, thus, it is unlikely in a position to transfer its proton to the activated C-atom (Fig. S15b). This is in contrast to MerB enzyme, where carboxylic group of Asp99 is located in close proximity to the Hg center at the active site of the enzyme and, thus possibly participates in proton transfer. Similarly, in the case of **9** or **10** (devoid of any acidic proton) we observed Me_2Hg formation (Figs S14 and S15b), suggesting that the presence of –SH group is extremely crucial for Hg–C protonolysis. Recently, Parkin *et al.* in their pioneer work reported the protolytic Hg–C bond cleavage of MeHgX (X = Cl or I) by **11** via an unknown reaction mechanism, when mercury alkyls MeHgX were heated with excess amount of **11** for overnight at high temperature (100 °C).[25] Unfortunately, N center being a hard base is unlikely to coordinate to the Hg center in the presence of mercurophilic Se center in the molecule and, as a result, **11** produces toxic Me_2Hg, instead of CH_4, in reaction with MeHgX at 21 °C (Fig. S16). It is noteworthy to mention here that imidazole-based biomolecule selenoneine, with two N–H protons in the heterocycle, was reported to detoxify $MeHg^+$ in a different pathway, i.e., through conversion of biologically inert HgSe species.[26] Recently, we have also shown that the imidazole-based thione/selone, having an $–N(CH_2)_2OH$ substituent, degrades various RHgOH *via* the formation of HgS/HgSe species.[27]

To understand the mechanism by which **1** facilitates the protolytic Hg–C bond cleavage we have performed detailed quantum chemical calculations.[10a,28] The mercurophilic Se center of **1** approaches toward MeHgI to produce **1**•••MeHgI adduct (RS-1), Fig 5a. In RS-1, the Hg and Se distance is 3.3 Å and < Me–Hg–I bond angle is 172°, indicating a weak interaction between **1** and MeHgI. As the Se center of **1** further approaches MeHgI and strongly activates the Hg–C bond at the transition state (TS-1), the –SH group of $–N(CH_2)_2SH$ substituent almost simultaneously or concurrently attacks at Hg center and transfers thiol proton to the activated C-atom of departed CH_3 group (Mechanism–II) with an activation energy barrier of 34.2 kcal mol^{-1} (Fig. 5c). This results the production of CH_4 and tri-coordinated Hg complex PS-1, a cleaved product, which slowly converts into a higher coordinated stable Hg complexes in solution (see synthetic procedure and Figs. S28-S32 in ESI†). The Gibbs free energy values of the reactions of product formation (PS-2 from the reactions of **1** and MeHgCl and PS-3 and PS-4 from the reactions of **1** and MeHgX, Scheme S6 and Fig. S38) and the corresponding K values (Tables S4 and S5) indicate that the protonolysis reactions by **1** are thermodynamically more favourable than its S analogue **1**. Moreover, the Hg–C bond protonolysis of MeHgCl by **1** occurs at a slower rate, than MeHgI, with higher activation energy barrier of 38.1 kcal mol^{-1} (TS-2).

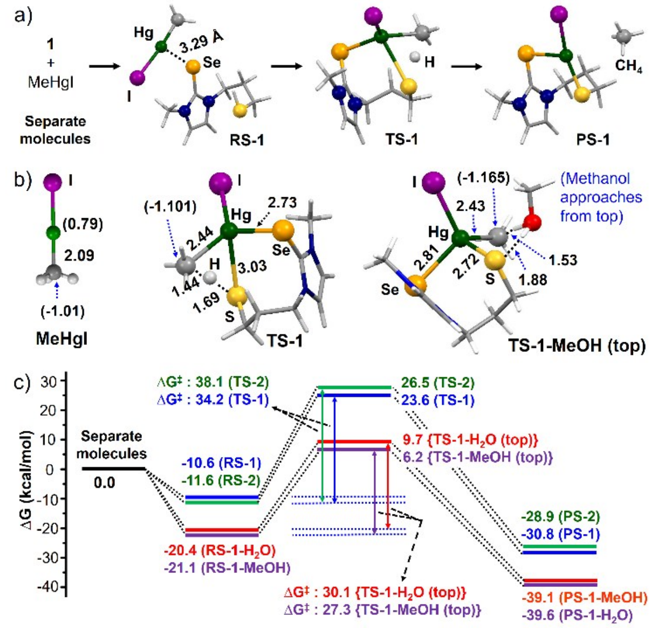


Fig. 5 (a) Reaction pathway of protonolysis of MeHgI by **1**. b) Optimized structures of MeHgI, TS-1, TS-1-MeOH (top). NPA atomic partial charge on C-atom of $–HgCH_3$ is mentioned in parentheses. Important distances (Å) are also mentioned. (c) The total energy profile of the reactions between **1** and MeHgX (X = I or Cl) in the presence or absence of solvents (MeOH and H_2O). All energies are in kcal mol^{-1}, relative to the free molecules. RS = reactant states; PS = product states; TS = transition states. RS-2, TS-2, and PS-2 correspond to the reaction of **1** and MeHgCl.

The Hg–C bond protonolysis of MeHgI by **1** or **2** was also investigated in the presence of protic solvents (MeOH-d_4, H_2O-d_2 or AcOH-d_4) to understand their role in assisting proton transfer to the activated C-atom. Interestingly, protonolysis of MeHgI by **2** increases with addition of protic solvent into the reaction solution in DMSO-d_6, in NMR tube (Figs S22-S27).[29] The protonolysis rate increases with decreasing the pK_a value of the protic solvent added into the reaction mixture (Initial rates ($M.h^{-1}$): 4.21 ± 0.21 x 10^{-3} in DMSO-d_6 only; 4.54 ± 0.19 x 10^{-3} in H_2O-d_2/DMSO-d_6; 5.20 ± 0.20 x 10^{-3} in MeOH-d_4/DMSO-d_6; 5.94 ± 0.16 x 10^{-3} in AcOH-d_4/DMSO-d_6). A significant increase of rate (6.52 ± 0.3 x 10^{-3} $M.h^{-1}$) is also observed when reaction is performed in a mixture of protic solvents, AcOH-d_4 and MeOH-d_4 (Fig. 6b). Because of the addition of deuterated protic solvent, we have observed both CH_4 and CH_3D peaks in ^1H NMR (Fig. 6a), indicating a solvent mediate proton transfer to the activated C-atom (Fig. S40).[30] DFT calculations on protic solvent assisted Hg–C protonolysis of MeHgI by **1** revealed that the solvent molecule, MeOH or H_2O, can approach in between the –SH and the activated –Me groups, either from the top (i.e., from the same side of iodine, as shown in TS-1-MeOH (top), Fig. 5b) or bottom (i.e., from the opposite side of iodine, as shown in TS-1-MeOH (bottom)), to facilitate the thiol proton transfer to the activated C-atom with low activation energy barriers. A substantially lower activation energy barrier was observed when the solvent molecule approaches from the top (Figs.

ChemComm Accepted Manuscript

Please do not adjust margins

Published on 20 May 2020. Downloaded by National University of Singapore on 5/24/2020 8:24:52 AM.

5b and S39). The values of the corresponding activation energy barriers for TS-1-MeOH (top), TS-1-MeOH (bottom), TS-1-H_2O (top), and TS-1-H_2O (bottom) are 27.3, 33.0, 30.1, and 33.1 kcal mol^{-1}, respectively. The charge on the departed C-atom is slightly more negative in TS-1 (-1.10) than MeHgI (-1.01), indicating that the leaving group in TS-1 is more susceptible to attack by an electrophilic thiol proton (Fig 5b).[10a,28] Moreover, the departing C-atom in TS-1-MeOH (top) (-1.17) possesses even more negative charge than in TS-1, which accounts for high reactivity in protic solvent. Furthermore, we noticed that the intramolecular proton transfer is far more effective than the intermolecular proton transfer–almost 80% demethylation of MeHgI was observed by **1**, whereas only 40% demethylation was observed by the combination of **4** and EtSH (external proton source), (Fig. 6c).

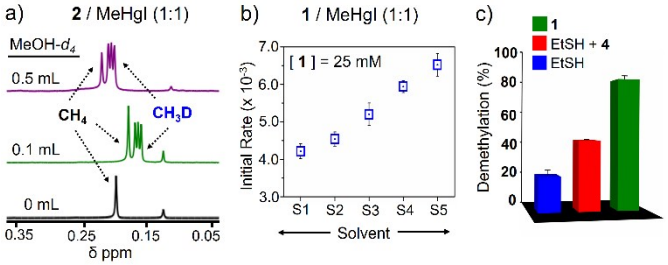


Fig. 6 (a) Formation of CH_4 and CH_3D in the reaction of **2**/MeHgI in DMSO-d_6/MeOH-d_4 solution (total volume = 0.6 mL). b) Protonolysis rates of MeHgI by **1** at 21 °C in DMSO-d_6 (S1) and in other solvent mixture, S2 (DMSO-d_6 : H_2O-d_2 = 5:1; [H_2O-d_2] = 5.5 mM), S3 (DMSO-d_6 : MeOH-d_4 = 5:1; [MeOH-d_4] = 3.1 mM), S4 (DMSO-d_6 : AcOH-d_4 = 5:1; [AcOH-d_4] = 1.7 mM), S5 (DMSO-d_6 : MeOH-d_4 : AcOH-d_4 = 4:1:1). c) Percentage of demethylation of MeHgI (25 mM) induced by EtSH (25 mM), **4** (25 mM)/EtSH (1:1), and **1** (25 mM) in DMSO-d_6 at 21 °C in 7 days.

Finally, we have investigated the ability of functional model of MerB, **1**, to protolytically cleave the Hg–C bond of biologically relevant organomercurials. To our delight, **1** is able to successfully cleave the Hg–Me or Hg–Et bonds in RHgCys (R = Me or Et) or thimerosal at room temperature with liberation of the corresponding CH_4 or C_2H_6 gas (Table 1 and Figs. S19-S21). Again, here we noticed that the Hg–Et bond protonolysis occurs at a faster rate than the Hg–Me bond protonolysis.

In summary, we report a synthetic compound **1**, with a large negative charge on Se center (selenolate character) and a –$N(CH_2)_3SH$ substituent at the ring, which facilitates protolytic Hg–C bond cleavage of various environmentally and biologically relevant organomercurials at room temperature, in the absence of any external proton source. Moreover, the protonolysis of Hg–C bond by **1** occurs at a faster rate in protic solvents than in aprotic solvent–more rapidly in AcOH than in MeOH (AcOH is more acidic than MeOH). This may be one of the possible reasons why Asp-containing MerB1 is more efficient in Hg–C protonolysis than Ser-containing MerB2 and, possibly, indicates that the Ser residue at the active site of MerB2 may assist in proton transfer (mechanism III). Our study is highly significant as it provides an insight of a new type of synthetic molecule which could potentially remove $MeHg^+$ from biomolecules and converts it into CH_4 and less toxic selone-Hg^{2+}-thiolate complex, similar to the bacterial enzyme organomercurial lyase MerB, which is absent in higher species like human.

We thank to James G. Omichinski for insightful comments on this work. RK, RD, RKR and AG thank to SNU for fellowship. We thank to SERB (SB/S1/IC-44/2013; CRG/2018/004591), government of India, for financial support.

CAUTION! *Organomercurials are extremely toxic, and thus appropriate safety precautions must be taken during experiments.*

Conflicts of interest

View Article Online
DOI: 10.1039/D0CC02232B

There are no conflicts to declare

Notes and references

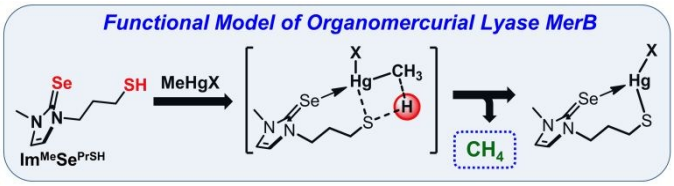
1 T. W. Clarkson, L. Magos, *Crit. Rev. Toxicol.,* 2006, **36**, 609.
2 (a) P. A. Nogara, C. S. Oliveira, G. L. Schmitz, P. C. Piquini, M. Farina, M. Aschner, J. B. T. Rocha, *Biochim. Biophys. Acta, Gen. Subj.,* 2019, **1863**, 1. (b) P. A. Nogara, M. Farina, M. Aschner, J. B. Rocha, *Chem. Res. Toxicol.,* 2019, **32**, 1459–1461.
3 D. A. Geier, P. G. King, B. S. Hooker, J. G. Dórea , J. K. Kern, L. K. Sykes, M. R. Geier, *Clinica Chimica Acta,* 2015, **444**, 212.
4 J. G. Omichinski, *Science,* 2007, **317**, 205.
5 J. Lafrance-Vanasse, M. Lefebvre, P. Di Lello, J. Sygusch, J. G. Omichinski, *J. Biol. Chem.,* 2009, **284**, 938.
6 H. M. Wahba, L. Lecoq, M. Stevenson, A. Mansour, L. Cappadocia, J. Lafrance-Vanasse, K. J. Wilkinson, J. Sygusch, D. E. Wilcox, J. G. Omichinski, *Biochemistry,* 2016, **55**, 1070.
7 T. P. Begley, A. E. Walts, C. T. Walsh, *Biochemistry*, 1986, **25**, 7192.
8 S. M. Miller, *Nat. Chem. Biol.*, 2007, **3**, 537.
9 H. Strasdeit. *Angew. Chem., Int. Ed.,* 2008, **47**, 828.
10 (a) J. M. Parks, H. Guo, C. Momany, L. Liang, S. M. Miller, A. O. Summers, J. C. Smith, *J. Am. Chem. Soc.*, 2009, **131**, 13278. (b) A. Asaduzzaman, D. Riccardi, A.T. Afaneh, S. J. Cooper, J. C. Smith, F. Wang, J. M. Parks, G. Schreckenbach, *Acc. Chem. Res.*, 2019, **52**, 379.
11 K. E. Pitts, A. O. Summers, *Biochemistry,* 2002, **41**, 10287.
12 H. M. Wahba, M. J. Stevenson, A. Mansour, J. Sygusch, D. E. Wilcox, J. G. Omichinski, *J. Am. Chem. Soc.*, 2017, **139**, 910.
13 C. C. Huang, M. Narita, T. Yamagata, G. Endo, *Gene*, 1999, **239**, 361.
14 M. F. Chien, M. Narita, K. H. Lin, K. Matsui, C. C. Huang, G. Endo, *J. Biosci. Bioengin.*, 2010, **110**, 94.
15 M. Wilhelm, S. Deeken, E. Berssen, W. Saak, A. Lützen, R. Koch, H. Strasdeit, *Eur. J. Inorg. Chem.*, 2004, 2301.
16 B. Ni, J. R. Kramer, R. A. Bell, N. H. Werstiuk, *J. Phys. Chem. A.*, 2006, **110**, 9451.
17 P. Barbaro, F. Cecconi, C. A. Ghilardi, S. Midollini, A. Orlandini, A. A. Vacca, *Inorg. Chem.*, 1994, **33**, 6163.
18 (a) J. G. Melnick, G. Parkin, *Science*, 2007, **317**, 225. (b) J. G. Melnick, K. Yurkerwich, G. Parkin, *Inorg. Chem.*, 2009, **48**, 6763.
19 T. Zhang, H. Hsu-Kim, *Nat. Geosci.*, 2010, **3**, 473.
20 (a) R. Karri, M. Banerjee, A. Chalana, K. K. Jha, G. Roy, *Inorg. Chem.*, 2017, **56**, 12102. (b) R. Karri, A. Chalana, B. Kumar, S. K. Jayadev, G. Roy, *Chem. A Eur. J.*, 2019, **25**, 12810.
21 (a) G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics*, 2010, **29**, 2176. (b) T. Higashi, H. Ando, S. Kusumoto, K. Nozaki, *J. Am. Chem. Soc.*, 2019, **141**, 2247.
22 (a) A. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.*, 1985, **83**, 735. (b) A. Reed, L. Curtiss, F. Weinhold, *Chem. Rev.*, 1988, **88**, 899.
23 (a) Y. Rong, A. Al-Harbi, B. Kriegel, G. Parkin, *Inorg. Chem.* 2013, **52,** 7172–7182. (b) B. S. Stadelman, M. M. Kimani, C. A. Bayse, C.D. McMillen, J.L. Brumaghim, *Dalton Trans.,* 2016, **45**, 4697–4711. (c) G. Roy, G. Mugesh, *J. Am. Chem. Soc.*, 2005, **127**, 15207.
24 M. Banerjee, G. Roy, *Inorg. Chem.*, 2017, **56**, 12739.
25 J. P. Palmer, G. Parkin, *J. Am. Chem. Soc.*, 2015, **137**, 4503.
26 M. Yamashita, Y. Yamashita, Handbook of Marine Biotechnology; Kim, S.-K., Ed.; Springer Berlin Heidelberg: Berlin, 2015, 1059.
27 (a) M. Banerjee, R. Karri, K. S. Rawat, K. Muthuvel, B. Pathak, G. Roy, *Angew. Chem., Int. Ed.,* 2015, **127**, 9455. b) M. Banerjee, R. Karri, A. Chalana, R. Das, K. S. Rawat, B. Pathak, G. Roy, *Chem. A Eur. J.*, 2017, **23**, 5696.
28 X. C. Li, R. Z. Liao, W. C. Zhou, G. *J. Chen, Phys. Chem. Chem. Phys.*, 2010, **12**, 3961.
29 E. Gopinath, T. C. Bruice, *J. Am. Chem. Soc.*, 1987, **109**, 7903.
30 F. A. Anet, D. J. O'Leary, *Tetrahedron Lett.*, 1989, **30**, 2755.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

View Article Online
DOI: 10.1039/D0CC02232B

Table of Content:



We report for the first time a synthetic organoselenium molecule $Im^{Me}Se^{PrSH}$, having an $–N(CH_2)_3SH$ substituent, which showed a unique ability to detoxify a wide variety of environmentally and biologically organomercurials (RHg^+) including thimerosal via Hg–C protonolysis in the absence of external thiol or acid (proton source) under mild conditions and, thus, acts as a functional model of MerB.

Published on 20 May 2020. Downloaded by National University of Singapore on 5/24/2020 8:24:52 AM.

ChemComm Accepted Manuscript