Mechanistic Aspects of the Gas-Phase Coupling of Thioanisole and Chlorobenzene to Dibenzothiophene Catalyzed by Atomic Ho$^+$

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Dedicated to Professor R. N. Zare, Stanford University, on the occasion of his 75th birthday.

Mechanistic aspects of the novel gas-phase generation of dibenzothiophene via coupling of thioanisole and chlorobenzene, employing atomic Ho$^+$ as a catalyst, have been investigated using Fourier-transform ion cyclotron resonance mass spectrometry in conjunction with density functional theory (DFT) calculations.

Introduction

Sulfur heterocycles are important building blocks of various chemical products, including organic thin-film transistors$^{1,2}$, metal extracting reagents$^{3,4}$, or bioactive and medicinally relevant compounds$^{5,8}$. Consequently, Methodological aspects related to the formation of organosulfur heterocyclic rings have attracted much attention. For the synthesis of sulfur-containing heterocycles usually metal sulfides, thioesters, or thioethers are employed as starting materials, and first- or second-row transition-metal complexes serve as catalysts. To achieve C–C$^9$–$^{12}$ or C–S$^{13,20}$ coupling involved in the ring closure process, activation of C–H$^{9,20}$, C–X (X = Br or I)$^{15,18,20}$ or C–S$^{14,17}$ bonds is a prerequisite. While gas-phase investigations proved helpful to obtain mechanistic aspects for numerous processes, except for a few reports on the formation of sulfur heterocycles in the gas phase$^{21}$, a more detailed understanding of the elementary steps is lacking.

In a previous study on the reactions of atomic Ln$^+$ with chlorobenzene$^{22}$, strong indications have been found that Ho$^+$ generates efficiently the insertion product Ho(C$_6$H$_5$)(Cl)$^+$ which then promotes HCl elimination in a secondary reaction with chlorobenzene; further, intriguing coupling processes have been observed in preliminary studies on consecutive reactions of Ln$^+$ with chlorobenzene and thioanisole in which Ho$^+$ exhibited the highest efficiency. Thus, we explored these reactions in more detail, and here we describe a gas-phase approach of sequential C–C and C–S coupling to generate dibenzothiophene by using thioanisole and chlorobenzene as substrates and exploiting atomic Ho$^+$ as a catalyst. Gas-phase studies employing atomic catalysts$^{23}$ recently regained interest$^{24}$ in the context of “single-atom catalysis”$^{25}$.

Results and Discussion

Coupling of thioanisole and chlorobenzene is achieved via two steps: First, Ho$^+$ reacts with thioanisole to produce an ionic precursor, which subsequently undergoes reaction with chlorobenzene to re-generate Ho$^+$ under the elimination of the neutral heterocyclic product.

1 Reactions of Ho$^+$ with Thioanisole

1.1 Ion/molecule Reactions of Ho$^+$ with Thioanisole
Three primary channels were observed in the thermal reaction of Ho$^+$ with thioanisole introduced via a leak valve at a stationary pressure of $p = 1.0 \times 10^{-5}$ bar, i.e. reactions (1) – (3); the overall efficiency amounts to 30%, relative to the collision rate$^{26}$.

\[
\begin{align*}
\text{Ho(C}_2\text{H}_5\text{S})^+ + \text{CH}_4 & \quad 86\% \quad (1) \\
\text{Ho}^+ + \text{C}_2\text{H}_5\text{SCH}_3 & \quad 6\% \quad (2) \\
\text{Ho(C}_2\text{H}_5\text{S})^+ + \text{CH}_3 & \quad 8\% \quad (3)
\end{align*}
\]

C–S bond activation is involved in all three channels; in addition, C–H bond activation takes place in reactions (1) and (3), respectively. Structural information on the cationic product ions as well as mechanistic aspects of these processes were obtained from DFT calculations. The potential-energy surfaces (PESs) together with structural data of the associated intermediates and transition structures are shown in Fig. 1 for the generations of Ho(C$_2$H$_5$S)$^+$ and Ho(C$_2$H$_5$)$^+$, and in Fig. 2 two alternative pathways for the formation of Ho(CH$_3$S)$^+$ are presented.

### 1.2 Pathways to form Ho(C$_2$H$_5$S)$^+$ and Ho(C$_2$H$_5$)$^+$

Several coordination modes, e.g. $\eta^2$ or $\eta^6$ coordination to the ring, attachment of the cation to the sulfur atom etc., have been taken into account for the generation of the encounter complex of Ho$^+$ with thioanisole; however, irrespective of all starting structures considered, as a result of the optimization, only 1 has been identified as encounter complex. In 1, Ho$^+$ is $\eta^2$ coordinated to the sulfur and the ipso- carbon atom of the phenyl ring. This intermediate serves as the starting point for all three reaction channels (1) – (3). Subsequent to the adduct formation, the generations of both Ho(C$_2$H$_5$S)$^+$ and Ho(C$_2$H$_5$)$^+$, reactions (1) and (2), proceed by the oxidative insertion of Ho$^+$ into the S–CH$_3$ bond thus forming intermediate 2. Since ground state Ho$^+$ possesses a 4$f^{11}$5$d^1$6$s^2$ electronic configuration, one 4$f$ electron of Ho$^+$ has to be promoted to a non-$\sigma$ valence orbital to allow the formation of 2 in which holmium is engaged in forming two $\sigma$ bonds. NBO analysis of the IRC coordinates of TS1/2 indicates that the electron promotion of Ho$^+$ from a 4$f$ orbital to a non-$\sigma$ valence orbital occurs after cleavage of the S–CH$_3$ bond. Thus, both the promotion energy (PE) of Ho$^+$ to attain a 4$f^{10}$5$d^1$6$s^1$ configuration (158 kJ/mol$^2$) as well as the S–CH$_3$ bond dissociation energy (BDE(S–CH$_3$), 278 kJ/mol$^{28}$) accompanied by distortion of the anisole molecule contribute to the energy barrier associated with TS1/2. While the homolytic cleavage of the Ho–CH$_3$ bond of intermediate 2 results in the formation of holmium benzenethiolate Ho(C$_2$H$_5$S)$^+$ (5), generation of Ho(C$_2$H$_5$)$^+$ (4) proceeds via a metal mediated $\sigma$-bond metathesis process 2 $\rightarrow$ 3, in which a hydrogen-atom transfer takes place from the ortho- position of the phenyl ring to the methyl group via TS2/3. Subsequently, the elimination of methane gives rise to the product ion 4. In line with the experimental results, both reactions are exothermic and thus energetically accessible under thermal conditions; moreover, the preferred elimination of CH$_4$ observed in the experiments, agrees with the more energy demanding cleavage of the Ho–CH$_3$ bond of 2, accompanied with the generation of Ho(C$_2$H$_5$)$^+$, as compared to the liberation of CH$_4$ along the sequence 2 $\rightarrow$ 3 $\rightarrow$ 4. Considering the relative energies of TS2/3 and TS1/2 (-87.9 kJ/mol versus -39.5 kJ/mol), insertion of Ho$^+$ into the S–CH$_3$ bond constitutes the rate-limiting step for the generation of the major product Ho(C$_2$H$_5$)$^+$.

### 1.3 Generation of Ho(CH$_3$S)$^+$

Two pathways have been located to produce Ho(CH$_3$S)$^+$. The first one commences with insertion of Ho$^+$ into the S–C$_2$H$_5$ bond, while in the second one the CH$_3$S group remains bound in the migration of Ho$^+$ to the top of the phenyl ring. As mentioned above, for the insertion process one electron of Ho$^+$ has to be promoted from a 4$f$ orbital to a non-$\sigma$ valence orbital; according to NBO analysis, the promotion takes place in proceeding from TS1/7 to intermediate 7 after cleavage of the S–C$_2$H$_5$ bond; then, again, one electron re-occupies the 4$f$ orbital of Ho$^+$ in the step TS7/8 $\rightarrow$ 8. In contrast, a 4$f$ $\rightarrow$ non-$\sigma$ promotion is not necessary for the pathway initiated by migration of the whole CH$_3$SHo$^+$ unit; here, throughout the reaction sequence 1 $\rightarrow$ 6 $\rightarrow$ 8 the holmium atom remains covalently bound only to the sulfur atom. Considering the comparable energies of TS1/6, TS1/7, and TS6/8, generation of Ho(CH$_3$S)$^+$ is influenced by several factors, including the BDE(C$_2$H$_5$–S) (357 kJ/mol$^{28}$), and...

![Fig. 1 PESs and structural information of the associated coordinates for the generations of Ho(C$_2$H$_5$S)$^+$ and Ho(C$_2$H$_5$)$^+$](image1)

![Fig. 2 PESs and structural information of the associated coordinates for the generation of Ho(CH$_3$S)$^+$](image2)
BDE(Ho\textsuperscript{+}SCH\textsubscript{2}–H), as well as the PE of Ho\textsuperscript{+} to attain a 4f\textsuperscript{10}5d\textsuperscript{1}6s\textsuperscript{1} configuration. Finally, compared to the formation of Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+}, the generation of Ho(CH\textsubscript{3})\textsuperscript{+} is energetically less favorable, in agreement with its lower branching ratio; also, the energetics for the generations of Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+} and Ho(CH\textsubscript{3})\textsuperscript{+} are in line with their similar branching ratios.

2 Reactions of Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+} with Chlorobenzene

For probing the thermal reactions of Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+} with chlorobenzene, the thermalized, mass-selected precursor Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+} is exposed to chlorobenzene which is introduced via a leak valve and present in the ICR cell at a stationary pressure of \( p = 1.0 \times 10^4 \) bar. The overall reaction efficiency amounts to 7\%, and three primary product channels were observed, i.e. reaction (4) – (6). Performing the same experiments without thermalization of the precursor Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+}, the branching ratio of reaction (6) increases up to 27\%, while the branching ratios of reaction (4) and (5) decrease to 63\% and 10\%, respectively.

The assignment of the [C\textsubscript{12}H\textsubscript{10}S\textsubscript{2}] unit as a dibenzo thiophene ligand (C\textsubscript{6}H\textsubscript{6}SC\textsubscript{6}H\textsubscript{6}) in the product ion of reaction (4) as well as for the neutral molecule of reaction (6) is based on the following considerations. First, if [C\textsubscript{12}H\textsubscript{10}S\textsubscript{2}] corresponds to an intact dibenzothiophene ligand, the generation of isomeric naphthothiophene is much more complicated starting from the two substrates employed in the experiments. The next and even more important aspect concerns the question if [C\textsubscript{12}H\textsubscript{10}S\textsubscript{2}] represents a single ligand, or if it is composed of two individual units, e.g. C\textsubscript{6}H\textsubscript{6}S and C\textsubscript{6}H\textsubscript{4}. To this end, the major product ion Ho[C\textsubscript{12}H\textsubscript{10}S\textsubscript{2}]\textsuperscript{+} has been mass selected and subjected to collision-induced dissociation (CID). At a collision energy \( E\text{coll} = 3.6 \) eV (given in the center-of-mass frame), Ho\textsuperscript{+} and Ho\textsuperscript{2+} are produced upon collision with argon in a ratio of about 9:1; applying lower collision energies, Ho\textsuperscript{+} corresponds to the only fragment ion generated. From the above results, the following conclusions can be drawn: (i) Ho[C\textsubscript{12}H\textsubscript{10}S\textsubscript{2}]\textsuperscript{+} corresponds to a complex with a single ligand which we assign to dibenzothiophene; the latter is generated in the reaction of thermalized Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+} with chlorobenzene under the elimination of HCl, and (ii) “bare” Ho\textsuperscript{+} is formed as product ion via the consecutive eliminations of HCl and dibenzothiophene.

Two chemically plausible pathways, (a) and (b), are proposed for the generation of Ho(C\textsubscript{6}H\textsubscript{6}SC\textsubscript{6}H\textsubscript{6})\textsuperscript{+} possessing a C\textsubscript{6}H\textsubscript{6}SC\textsubscript{6}H\textsubscript{6} ligand as illustrated in Scheme 1; both routes are initiated by σ bond metathesis under cleavage of the Ho–S and Ho–C bonds of the complex Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+}, respectively. The PESs and the structural information of the associated intermediates and transition structures for the two pathways are shown in Fig. 3, and the encounter complex 9 serves as a common starting point. The TS for the Ho–S bond cleavage (TS9/10) is much higher in energy relative to the entrance channel as well as to the alternative Ho–C bond cleavage proceeding via TS9/11 (61.7 kJ/mol versus -17.5 kJ/mol, i.e. dehydrochlorination is accessible under thermal conditions only via path (b) (9 – TS9/11 – 11); therefore, it is only this route which has been considered further in the calculations of the subsequent reaction steps. The reason for the much higher barrier of the Ho–S bond cleavage (TS9/10) as compared to the Ho–C bond (TS9/11) is probably related to the stronger Ho–S bond compared to the Ho–C bond reflecting electronegativity differences between sulfur and carbon; unfortunately, the respective bond-dissociation energies are

![Scheme 1 Plausible pathways for the generation of Ho(C\textsubscript{6}H\textsubscript{6}SC\textsubscript{6}H\textsubscript{6})\textsuperscript{+}.](image)

![Fig. 3 PESs and structural information of the associated coordinates for the initial Ho–C and Ho–S cleavages of Ho(C\textsubscript{6}H\textsubscript{6})\textsuperscript{+} upon its reaction with chlorobenzene. Selected bond lengths are given in Å; charges are omitted for the sake of clarity.](image)
not reported in the literature.

Subsequent to the formation of intermediate 11, dehydrochlorination proceeds either directly via a hydrogen atom transfer from an ortho- position of the phenyl ring to the chloride ligand (11 → 12), or may be preceded by hydrogen scrambling within the original chlorobenzene entity (11 → 13 → 14 → 15 → 16). The PESs for these processes and structural information of the associated intermediates and transition structures for the generation of Ho(C₅H₄SC₅H₄)⁺ as well as the intermediates for hydrogen scrambling along 13 → 16 are shown in Fig. 4; structural details of the transition structures involved in the hydrogen scrambling are given in ESI†. According to the calculations, hydrogen scrambling is less energy demanding than the loss of HCl. The H/D scrambling has been verified by labeling experiments: in the reactions of Ho(C₅H₄S)⁺ with 3,5-d-¹-chlorobenzene and 4-d-¹-chlorobenzene, eliminations of both HCl and DCl are observed for either substrate; the ratios of HCl/DCl elimination from 3,5f and 4d eliminate of both HCl and DCl are observed for either substrate; the ratios of HCl/DCl elimination from 3,5f and 4d are given in ESI†. According to the calculations, hydrogen scrambling is less energy demanding than the loss of HCl. The H/D scrambling has been verified by labeling experiments: in the reactions of Ho(C₅H₄S)⁺ with 3,5-d-¹-chlorobenzene and 4-d-¹-氯化苯, eliminations of both HCl and DCl are observed for either substrate; the ratios of HCl/DCl elimination from 3,5f and 4d are shown in Fig. 4; structural details of the transition structures involved in the hydrogen scrambling are given in ESI†. According to the calculations, hydrogen scrambling is less energy demanding than the loss of HCl. The H/D scrambling has been verified by labeling experiments: in the reactions of Ho(C₅H₄S)⁺ with 3,5-d-¹-氯化苯 and 4-d-¹-氯化苯, eliminations of both HCl and DCl are observed for either substrate; the ratios of HCl/DCl elimination from 3,5f and 4d are shown in Fig. 4; structural details of the transition structures involved in the hydrogen scrambling are given in ESI†. According to the calculations, hydrogen scrambling is less energy demanding than the loss of HCl. The H/D scrambling has been verified by labeling experiments: in the reactions of Ho(C₅H₄S)⁺ with 3,5-d-¹-氯化苯 and 4-d-¹-氯化苯, eliminations of both HCl and DCl are observed for either substrate; the ratios of HCl/DCl elimination from 3,5f and 4d are shown in Fig. 4; structural details of the transition structures involved in the hydrogen scrambling are given in ESI†. According to the calculations, hydrogen scrambling is less energy demanding than the loss of HCl. The H/D scrambling has been verified by labeling experiments: in the reactions of Ho(C₅H₄S)⁺ with 3,5-d-¹-氯化苯 and 4-d-¹-氯化苯, eliminations of both HCl and DCl are observed for either substrate; the ratios of HCl/DCl elimination from 3,5f and 4d are shown in Fig. 4; structural details of the transition structures involved in the hydrogen scrambling are given in ESI†. According to the calculations, hydrogen scrambling is less energy demanding than the loss of HCl. The H/D scrambling has been verified by labeling experiments: in the reactions of Ho(C₅H₄S)⁺ with 3,5-d-¹-氯化苯 and 4-d-¹-氯化苯, eliminations of both HCl and DCl are observed for either substrate; the ratios of HCl/DCl elimination from 3,5f and 4d are shown in Fig. 4; structural details of the transition structures involved in the hydrogen scrambling are given in ESI†. (see Fig. 4); both processes are accessible at thermal conditions. Thus, according to the calculation, the observed ionic product Ho(C₅H₄SC₅H₄)⁺ may correspond to a mixture of 17 and 19. Regarding the formation of Ho⁺ + HCl + C₅H₄SC₅H₄, reaction (6), this has been calculated to be higher in energy by 25 kJ/mol as compared to the entrance channel, i.e. Ho(C₅H₄S)⁺ + C₅H₄Cl, and should thus not be observed under thermal conditions. Thus, assuming that the ions in the experiments are thermalized to room temperature possessing a kinetic energy of 3RT = 7.4 kJ/mol at 298 K, theory overestimates the relative energy of the exit channel.

Considering the overall process, i.e. Ho⁺ + C₅H₄SCH₃ + C₅H₄Cl → Ho⁺ + HCl + C₅H₄SC₅H₄, the atomic holmium cation Ho⁺ serves as a catalyst, as illustrated in Scheme 2. However, the turnover number is limited by side reactions with both substrates (processes (2), (3), and (5)), and the turn-over frequency is diminished due to the inefficient release of the neutral coupling product from 19 under the regeneration of Ho⁺ ions to initiate the next catalytic cycle. As so often in heterogeneous catalysis, product release and regeneration of the active catalyst (i.e. Ho⁺) requires external energy. In addition, the presence of both substrates

![Diagram](image)
thioanisole and chlorobenzene at the same time in a “one-pot synthesis” allows for additional side reactions as Ho$^+$ can react with both precursors. Moreover, Ho(C$_3$H$_7$)$_2$ can also react further with thioanisole to give higher order products. Thus, timing of the interaction of the catalyst with the two substrates needs to be well designed to improve the efficiency of the coupling process.

Conclusion

In this work, we present a novel gas-phase coupling of thioanisole and chlorobenzene to dibenzothiophene catalyzed by “bare” holmium cation Ho$^+$ and we address mechanistic aspects by DFT calculations and labeling experiments. The coupling is achieved via a two-step reaction: the first one corresponds to the reaction of Ho$^+$ with thioanisole to generate Ho(C$_3$H$_7$)$_2$; subsequently, Ho(C$_3$H$_7$)$_2$ reacts with chlorobenzene to produce the final products. A combination of experimental and computational investigations, provides insight into the most likely reaction mechanisms. For the overall transformation, atomic Ho$^+$ serves as a catalyst which, however, is also engaged in side reactions with both substrates. Similar to heterogeneous catalysis, external energy is required to release the coupling product from the catalyst.

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Notes and references