Mechanistic Insights for Dimethyl Sulfoxide Catalyzed Aromatic Chlorination Reactions

Zheng-Wang Qu,[a] Hui Zhu,[a] and Stefan Grimme[a]

Recently, the dimethyl sulfoxide O–SMe₂ catalyzed aromatic chlorination reaction using N-chlorosuccinimides (NCl) under mild conditions has proven useful for bioactive compounds potentially containing various functional groups such as amide and hydroxyl. A novel catalytic mechanism is revealed by extensive DFT calculations using the anisole PhOMe as electronic-rich model substrate. The Cl⁺ transfer from NCl to O–SMe₂ slowly reacts via the S-chloro sulfoxonium O–SClMe₂⁺ to the S-chloro ylide O–SClMeCH₂, followed by facile Cl⁺ transfer from NCl to the ylide CH₂⁺ site to initialize efficient electrophilic Cl⁺ transfer to nucleophilic substrates. According to the new proposal, the polarizable S and electronegative O sites of O–SMe₂ may act as efficient Cl⁺ and H⁺ shuttles, respectively, in catalytic aromatic chlorination. If O–SMe₂ is present in high concentration, it can trap intermediate SMe₂OH⁺ into a stable H⁺-bound dimer (SMe₂O₂)H⁺ to inhibit efficient protic NCl activation. These mechanistic insights may be generally useful for the rational design of novel dual functional halonium transfer catalysts.

Chlorinated aromatic compounds are very useful building blocks in organic synthesis,[1] extensively used as precursors of common organometallic reagents as well as crucial substrates of transition-metal-catalyzed coupling reactions.[2] The introduction of chloro group can widely modulate the electronic, lipophilic, and steric properties of the attached frameworks and hence is important in many research fields[3] such as pharmaceutical and material science as both functional and functionalizable molecules.[4] In fact, hundreds of aryl chlorides have been approved as clinical drugs so far, typically prepared by iterative synthesis with pre-chlorination. However, post-synthetic modification of drug-like molecules by aromatic chlorination is usually challenging due to various coexisting functional groups such as hydroxyls, amides and amines that require selective chlorinating reagents under mild conditions,[5] though enzyme-catalyzed chlorination of some structurally specified bioactive molecules are known.[6]

Recently, the guanidine-based Palau’chlor reagent[7] and non-symmetric iodanes[8] have been proven useful for the late-stage chlorination of various bioactive molecules and natural products. Efficient and practical late-stage chlorination of (hetero)arenes, drugs, natural products and peptides has also been achieved using dimethyl sulfoxide (DMSO, or O–SMe₂) as a novel catalyst and N-chlorosuccinimide (NCl) as a cheap chlorinating reagent under neutral conditions in chloroform solution at room temperature.[9] The O-chloro sulfinium SMe₂OCI⁺ was proposed as the key intermediate for electrophilic Cl⁺-transfer, which can be further trapped by concentrated O–SMe₂ into stable Cl⁺-bound dimer (SMe₂O₂)Cl⁺ that may inhibit the catalysis (Scheme 1).[10] Similar O-bound halogen and chalcogen cations SMe₂OX⁺ and (SMe₂O₂)X⁺ (X=Br, I, SAr and SeAr) have also been suggested as reactive reagents accumulated in electrochemical cation pool.[10] Though widely used as a polar aprotic solvent, O–SMe₂ may react as nucleophile via the oxygen or more polarizable sulfur centers.

[1] Dr. Z.-W. Qu, Dr. H. Zhu, Prof. S. Grimme
Mulliken Center for Theoretical Chemistry,
University of Bonn
Beringstr. 4, 53115 Bonn (Germany)
E-mail: qu@thch.uni-bonn.de

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Recent proposal for DMSO as catalyst (Jiao et al., 2019)

1. O-chloro cation SMe₂Cl⁺ for Cl⁺ transfer
2. Catalyst trapping via Cl⁺ bound (SMe₂O₂)Cl⁺

This DFT mechanistic work:

1. Methyl chlorination aided initializing;
2. S-site as efficient Cl⁺ shuttle;
3. O-site as efficient H⁺ shuttle: potential trapping via H⁺-bound (SMe₂O₂)H⁺.

Scheme 1. Recently proposed (top) and our new DFT-based (bottom) mechanism for the O–SMe₂ catalyzed electrophilic aromatic chlorination by N-chlorosuccinimides NCl. The DFT calculations highlight the coupled methyl chlorination of O–SMe₂ in initializing electrophilic Cl⁺ transfer from S-chloro sulfoxonium O–SClMe₂⁺ with the respective S and O sites of O–SMe₂ acting as efficient Cl⁺ and H⁺ shuttles during the catalysis.
When activated by suitable electrophiles such as acetic anhydride, O=SMe₂ may also act as a mild oxidant and even as an useful nucleophilic ylide reagent after methyl deprotonation. The novel catalytic behavior of ambient O=SMe₂ in electrophilic aromatic chlorination thus deserves a more detailed mechanistic analysis.

In this work, state-of-the-art DFT calculated free energies at the PW6B95-D3 + COSMO-RS/TPSS-D3 + COSMO level in chloroform solution (see below for computational details) are used to explore the mechanism of the O=SMe₂-catalyzed chlorination of anisole PhOMe (PoH, with H highlighting the para-hydrogen atom) using NsCl as a chlorinating reagent (Scheme 1). In contrast to recent mechanistic proposals, our DFT calculations clearly show that the Cl⁺ transfer from NsCl to transient S-chloro ylide O=SClMeCH₂ is crucial to initialize efficient electrophilic Cl⁺ transfer to nucleophilic substrates, with the O and more polarizable S sites of O=SMe₂ acting as efficient H⁺ and Cl⁺ shuttles, respectively, in catalytic aromatic chlorination using NsCl. The stable H⁺-bound dimer (SMe₂O)Cl⁺ instead of the recently proposed (SMe₂Cl)₂⁺ complex is formed in concentrated O=SMe₂ solution that may effectively inhibit the efficient regeneration of catalytic S-chloro sulfoxonium O=SClMe₂⁺ via protic NsCl activation.

As shown in Figure 1, the initial chloronium Cl⁺ transfer from NsCl to O=SMe₂ may be directed by the moderately strong intermolecular N–Cl–S and N–Cl–O non-covalent (halogen bond) interactions. Despite 2.5 kcal/mol stronger N–Cl–O than N–Cl–S halogen bond is involved, the Cl⁺ transfer to the O-site of O=SMe₂ is endergonic by 50.3 kcal/mol in chloroform solution thus highly unlikely, in sharp contrast to the recent mechanistic proposal with the O-chloro sulfoxonium O=SClMeOCl⁻ key intermediate for electrophilic Cl⁺ transfer. On the other hand, the Cl⁺ transfer from NsCl to the more polarisable S-site of O=SMe₂ is only 20.5 kcal/mol endergonic to form the S-chloro sulfoxonium O=SClMe₂⁺, which after a methyl α-deprotonation with separated anion Ns⁻ over a free energy barrier of 24.1 kcal/mol (via transition structure TS1) may lead to the meta-stable ylide O=SClMeCH₂ (along with stable succinimide NsH) that is still 2.4 kcal/mol higher in free energy. Further Cl⁺ transfer from NsCl to the ylide CH₂ site of O=SClMeCH₂ is —2.1 kcal/mol exergonic over a lower barrier of 16.1 kcal/mol (via TS2) to form the reactive S-chloro sulfoxonium O=SClMe₂⁺Cl⁺ (along with separated Ns⁻), which is now almost neutral in free energy with respect to the initial reactants of NsCl and O=SMe₂. The newly formed S–Cl single bond within S-chloro sulfoxonium is much weaker than the old N–Cl bond of NsCl thus may enable further Cl⁺ transfer to aromatic substrates.

To understand the solution structures of DMSO-stabilized halogen and chalcogen cations X⁺ (F, Cl, Br, I, SPh, SePh), the X⁺ affinities (binding free energies) at both the central S and the terminal O sites are also computed, with the S-bound sulfoxonium O=SClMe₂⁺ structures being consistently more stable than the O-bound sulfoxonium O=SClMeO⁻ structures by 75.2, 29.8, 21.0, 7.6, 6.2 and 2.6 kcal/mol, respectively. The higher X⁺ affinities at the central S-site can be further enhanced by about 3 ~ 4 kcal/mol in more polar DMSO solution, though no stable Cl⁺-bonded halogen bond dimer (O=SMe₂)₂Cl⁺ could

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**Figure 1.** DFT computed free energy paths (in kcal/mol, at 298 K and 1 M concentration) for the reaction of NsCl and O=SMe₂ in chloroform solution, forming reactive S-chloro sulfoxonium O=SClMe₂⁺ (along with separated anion Ns⁻) for further Cl⁺ transfer to nucleophilic substrates. The crucial C, H, O, N, S and Cl atoms in ball-and-stick models are highlighted by grey, white, red, blue, yellow and green balls, while partially breaking bonds indicated by dashed lines, with selected bond lengths shown in red numbers in Å. Note that the endergonic Cl⁺ transfer from NsCl to the S-site of O=SMe₂ is compensated by exergonic methyl deprotonation and chlorination of O=SMe₂.
be found in solution. In contrast, the O-protonated sulfonium SMelOH\(^+\) is found to be 24.1 kcal/mol more stable than the S-protonated sulfonium O\(\equiv\)SMe\(_2\)\(^-\), and can be further stabilized by 1 mol/L concentrated O\(\equiv\)SMe\(_2\) in chloroform solution into the H\(^-\)bound dimer (SMe\(_2\)O\(\cdot\)H\(^+\)) that is \(-7.3\) kcal/mol more stable (see ESI). Our DFT calculations strongly support the central S and the terminal O sites of O\(\equiv\)SMe\(_2\) as potential halonium X\(^-\) and proton H\(^+\) shuttles, respectively.

Facile Cl\(^-\) transfer from the sulfonium O\(\equiv\)SClMe\(_2\)Cl\(^-\) to O\(\equiv\)SMe\(_2\) may occur directly via the S–Cl–S halogen bond complex O\(\equiv\)SClMe\(_2\)Cl\(_2\) (Fig. S1) with the catalytic S-chlorosulfonium O\(\equiv\)SClMe\(_2\)\(^-\) along with the methyl-chlorinated by-product O\(\equiv\)SClMe\(_2\)Cl. Starting from the neutral ylide O\(\equiv\)SClMe\(_2\)Cl\(^-\), Cl\(^-\) elimination from the S-site followed by Cl\(^-\) addition to the CH\(_2\) site may also lead to O\(\equiv\)SMe\(_2\)Cl, which is however kinetically 5.5 kcal/mol less favourable than the above NsCl-promoted conversion. Facile α-deprotonation of O\(\equiv\)SClMe\(_2\)Cl\(^-\) with the coexisting anion Ns\(^-\) may lead to another ylide O\(\equiv\)SClMe\(_2\)Cl\(^-\) that can also easily abstract Cl\(^-\) from NsCl to initialize efficient electrophilic Cl\(^-\) transfer to nucleophilic substrates (along with further methyl chlorination of O\(\equiv\)SClMe\(_2\)Cl, see ESI). Note that the sizable overall barrier of 24.1 kcal/mol (via TS1) found for the formation of by-product O\(\equiv\)SClMe\(_2\)Cl along with the catalytic sulfonium O\(\equiv\)SClMe\(_2\)\(^-\) is consistent with the slow methyl chlorination of O\(\equiv\)SMe\(_2\) with NsCl observed in experiment,\(^[13]\) thus providing further support to our DFT-computed reaction mechanism.

As shown in Figure 2 (A), the electrophilic Cl\(^-\) transfer from S-chlorosulfonium O\(\equiv\)SClMe\(_2\)\(^-\) to the aromatic substrate PoH is only 2.8 kcal/mol endergonic over a low barrier of 11.3 kcal/mol to form the arenium PoHCl\(^+\) (along with neutral O\(\equiv\)SMe\(_2\) ),

![Figure 2. DFT computed free energy paths (in kcal/mol) at 298 K and 1 M concentration) in chloroform solution for: (A) the electrophilic chlorination of anisole PHoMe (PoH) using catalytic S-chlorosulfonium O\(\equiv\)SClMe\(_2\)\(^-\); (B) the protic activation of NsCl with the sulfonium SMelOH\(^-\) for the regeneration of O\(\equiv\)SClMe\(_2\)\(^-\) to complete the catalytic cycle. The crucial C, H, O, N, S and Cl atoms in ball-and-stick models are highlighted by grey, white, red, blue, yellow and green balls, while partially breaking bonds indicated by dashed lines, with selected bond lengths shown in red numbers in Å. Note that 1 M concentrated O\(\equiv\)SMe\(_2\) may trap the sulfonium intermediate SMelOH\(^-\) by 7.3 kcal/mol to form stable dimeric (SMelCl)\(^+\), H\(^+\) thus effectively inhibit the efficient protic NsCl activation.](image-url)
O–SClMe\textsuperscript{+}; the conversion from HNs into stable NsH is −15.2 kcal/mol exergonic and almost barrierless via double-H-bonded dimer (HNs\textsubscript{2}), eventually making the protic NsCl activation both kinetically and thermodynamically feasible to complete the catalytic cycle of electrophilic aromatic chlorination. The catalytic cycle consists of two efficient steps: the electrophilic Cl\textsuperscript{−} transfer from O=SClMe\textsuperscript{+} to PoH substrate over a low 11.3 kcal/mol barrier and the facile SMeOH\textsuperscript{−}-promoted NsCl activation over a higher barrier of 15.8 kcal/mol. Note that though the highly basic Ns\textsuperscript{−} counter-anion may deprotonate HO=SMMe\textsuperscript{−} to interrupt the O=SClMe\textsuperscript{+} mediated catalysis, the catalytic cycle can be reinitialized via the methyl chlorination of O=SMMe with NsCl.

When 1 mol/L concentrated O=SMMe\textsuperscript{+} is additionally present in solution, the intermediate SMMeOH\textsuperscript{−} can be trapped into the O−H−O hydrogen bonded dimer (SMMe\textsubscript{2}O\textsubscript{2})H\textsuperscript{+} that is 7.3 kcal/mol more stable in chloroform solution, effectively increasing the protic NsCl activation barrier to about 23.1 kcal/mol. In pure O=SMMe\textsuperscript{+} solution, such barrier can be further enhanced due to even stronger trapping of SMMeOH\textsuperscript{−}, eventually inhibiting efficient NsCl activation. These results are consistent with the almost inhibited catalysis in DMSO solution.[19] In cases of substrates with basic amine functional group, the amine group may act as proton shuttle instead but this will not change the crucial role of the S-site of DMSO as efficient Cl\textsuperscript{−} shuttle.

In summary, a novel mechanistic picture is revealed by extensive DFT calculations for the O=SMMe\textsuperscript{+} catalyzed electrophilic chlorination of the anisole PoH using NsCl as practical chlorinating reagent. The meta-stable S-chloro ylide O=SClMeCH\textsubscript{3} is slowly formed in the reaction of NsCl and O=SMMe\textsuperscript{+} followed by facile Cl\textsuperscript{−} abstraction from NsCl to initialize efficient Cl\textsuperscript{−} transfer from catalytic sulfonium O=SClMe\textsuperscript{+} to nucleophilic substrates, with the O and more polarizable S sites of O=SMMe acting as efficient H\textsuperscript{+} and Cl\textsuperscript{−} shuttles, respectively. The formation of stable (SMMe\textsubscript{2}O\textsubscript{2})H\textsuperscript{+} in concentrated O=SMMe\textsuperscript{+} may inhibit the regeneration of O=SClMe\textsuperscript{+} via efficient protic NsCl activation. These mechanistic insights can be very useful for electrophilic transfer of other halogen and chalcogen cations.

**Computational Methods**

All DFT calculations are performed with the TURBOMOLE 7.3 suite of programs[12-18] The structures are fully optimized at the TPSS-D3/def2-TZVP + COSMO(CHCl\textsubscript{3}) level, which combines the TPSS meta-GGA density functional[19] with the B3-damped DFT-D3 dispersion correction[16] and the def2-TZVP basis set,[13] using the Conductor-like Screening Model (COSMO)[10] for CHCl\textsubscript{3}, solvent (dielectric constant ε = 4.8 and diameter R\textsubscript{solvent} = 3.17 Å). The well-established density-fitting RI-J approach[11,17] is used, which speeds up semi-local DFT functional calculations by a factor of 5–20 at practically no loss of accuracy. Chemically reasonable reaction paths are generated manually and tested in DFT calculations. Useful initial guesses of transition structures are obtained from interpolation between optimized reactant/intermediate/ product structures and constrained optimizations with appropriate reaction coordinates. The optimized structures are characterized by frequency analysis (no imaginary frequency for true minima and only one imaginary frequency for transition states) to provide thermal free-energy corrections (at 298.15 K and 1 atm) according to the modified ideal gas-rigid rotor-harmonic oscillator model.[20] The connection of the transition state with reactants and products is checked visually by carefully examining the vibrational transition mode.

More accurate solvation free energies in CHCl\textsubscript{3} are computed with the COSMO-RS model[18] (parameter file: BP_TZVP_C30_1601.ctd) using the COSMOTHERM package[21] based on the TPSS-D3 optimized structures, corrected by +1.89 kcal/mol to account for the 1 mol/L reference concentration in solution. To check the effects of the chosen density functional on the reaction energies and barriers, single-point calculations at both TPSS-D3[13] and hybrid-meta-GGA PW6B95-D3[21] levels are performed using the large def2-QZVP[13] basis set. Final reaction free energies (ΔG) are determined from the electronic single-point energies plus TPSS-D3 thermal corrections and COSMO-RS solvation free energies. The reaction energies from both DFT functionals are in good mutual agreement with average deviations of only 0.7 ± 2.7 (average ± standard deviation) kcal/mol, with the TPSS-D3 functional tends to predict somewhat lower reaction barriers but stronger halogen bond interactions (see ESI). In the discussion, the more reliable PW6B95-D3 + COSMO-RS free energies (in kcal/mol, at 298.15 K and 1 mol/L standard state concentration) are used unless specified otherwise. The applied DFT methods in combination with the large AO basis sets provide usually accurate electronic energies with typical errors of 1–2 kcal/mol for chemical energies (including barriers), which has been tested thoroughly for the huge data base GMTKN55[22] that is the common standard in the field of DFT benchmarking.

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**Conflict of Interest**

The authors declare no conflict of interest.

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