Highlight

Quantum hydrogen tunneling promoting halogen-atom and group transfer chemistry

Xiao Xiao [a], Yi-Ping Yao [a], Biao Chen [a], Chuan Xiang Alvin Tan [b], Fen-Er Chen [a,c,d,*]

[a] Institute of Pharmaceutical Science and Technology, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, China
[b] Department of Chemistry, National University of Singapore, 3 Science Drive 3 117543, Singapore
[c] Engineering Center of Catalysis and Synthesis for Chiral Molecules, Fudan University, Shanghai 200433, China
[d] Shanghai Engineering Center of Industrial Asymmetric Catalysis for Chiral Drugs, Shanghai 200433, China

ABSTRACT

A quantum-hydrogen-tunneling-controlled halogen-atom and group transfer strategy has been successfully developed to generate carbon radicals by using the substituted cyclohexadiene as the abstractor under mild photochemical conditions, in which alkyl and aryl halides as well as numerous alcohol and thiol analogues can be activated. Mechanism investigation unveiled that this process is inhibited from thermodynamic and kinetic effects but is rendered successful through quantum tunneling.

Halogen-atom and group transfer strategies have been extensively utilized in classical carbon radical chemistry, in which halides and alcohol or thiol derivatives feature commercial availability or otherwise facile accessibility. The canonical approaches of halogen-atom transfer follow three reactivity principles (Fig. 1A): (1) In this process, a collinear arrangement among the three atoms (*i.e.*, C, X, and Y) is relied on, leading to realizing maximum orbital overlap between the C−X antibonding orbital (σ*) and the abstracting radical (Y•) singly occupied molecular orbital (SOMO). (2) In order to ensure a thermodynamically favorable process, the original C−X bond in the substrate requires to be weaker than the Y−X bond. (3) Rapid kinetics ensuing from the interaction of polar effects at the transition state would reduce the reaction barriers via charge transfer. This conventional process for carbon radical generation is routinely assisted by the nucleophilic tin and silicon radicals, which possess the defects of toxicity, cost, and waste management [1]. Hence, the development of a novel and economic strategy that is independent of these three principles to achieve the halogen-atom transfer remains highly desired and sought after.

Tunneling is a basic quantum mechanical property that enables particles to surmount potential energy barriers in spite of lacking the energy to conquer them [2–4]. This principle is directly correlated with the wave nature of particles, leading them to penetrate their surrounding potential energy barriers. In chemical transformations, this effect generally exists in the case of electrons and is also common for the hydrogen, or hydride atoms and protons transfer. Furthermore, the hydrogen atom (H•) is an ideal and economic species towards the halogen-atom transfer from both thermodynamic (enthalpic) and kinetic (polar) features (Fig. 1A). Experimentally, the greatest challenge to access this mode for halogen abstraction is to fulfil the generation of naked H•.

To solve this difficulty, Lakhdar, Leonori and coworkers turned the contemplation to the concept of proaromaticity, which has been widely utilized for the formation of silicon radicals (Fig. 1B) [5]. In this strategy, a synthetic Me₃Si-containing cyclohexadiene derivative **2** is essential, which could be activated by H-atom transfer (HAT) to furnish the cyclohexadienyl radical **3**. A thermodynamically favorable aromatization process subsequently occurred, resulting in the release of the versatile Me₃Si• species that can be utilized in numerous types of radical chain propagations and achieving the halogen-atom and group transfer chemistry. Similarly, the authors hypothesize the simple cyclohexadiene radical **4•** would realize the synthesis of reactive radical H• with the mentioned process.

Recently, this hypothesis was validated *via* the valuable dehalogenation reaction, in which the available cyclohexadiene derivative γ-terpinene promoted a quantitative debromination of **5a** (X = Br) to obtain **22a** under mild photoredox conditions with the assistance of the organic dye 4CzIPN as the photocatalyst, NaCl or NaN₃ as an additive,
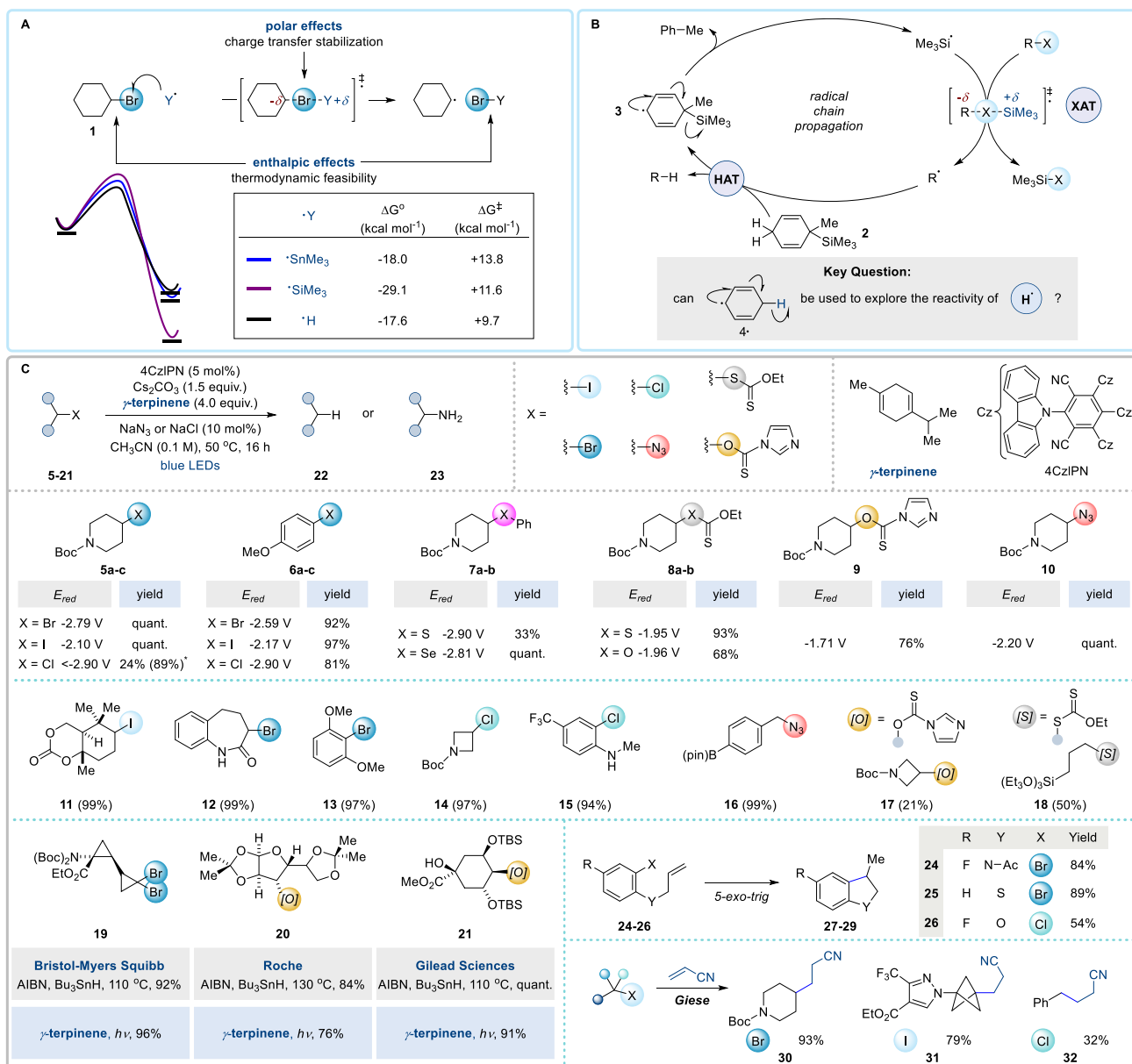
Fig. 1. Quantum hydrogen tunneling promoting halogen-atom and group transfer chemistry. (A) The general mechanism for halogen-atom transfer reactions and computational studies on three model bromine-atom abstractions. (B) Si-containing proaromatic cyclohexadienyl radicals that generate silicon radicals by fragmentation. XAT = halogen-atom transfer. (C) A γ-terpinene–mediated radical generation by halogen-atom and group transfer. *Yield obtained using Ir(ppy)$_3$ as the photocatalyst.

acetonitrile as the solvent, and blue light-emitting diode (LED) as the irradiation (Fig. 1C) [6]. Moreover, the utilization of analogous scaffolds to replace γ-terpinene, such as 1,4-cyclohexadiene, could gain similar experimental results. This strategy was compatible with the corresponding C-4 iodide (**5b, 11**) and, notably, chloride (**5c, 14**), as well as deactivated and electron-rich aryl halides (**6a-c, 13** and **15**). Significantly, the authors also successfully achieved group transfer settings, where the defunctionalization of C-4 sulphide (**7a**), selenide (**7b**), xanthate (**8a, 18**), and alcohol derivatives (**8b, 9** and **20–21**) could obtain the desired product **22** in moderate to excellent yields. Furthermore, alkyl azides (**10, 16**) were smoothly employed, leading to the formation of corresponding primary amines **23**. In other words, numerous functional groups, such as unprotected alcohol and amine, acetal, aldehyde, ketone, ester, lactam, Bpin, allyl, and heterocycle, were compatible in this process. The generated radical was also readily engaged to implement other mode transformations, such as reductive

5-*exo-trig* cyclizations and Giese additions. Taken together, this reaction was tolerant to all substrates that the classical activation strategy of tin and silicon radical chemistry was invariably used, and therefore bypassed the SET activation mechanism.

Next, the possible reaction mechanism was investigated by a series of experiments. Firstly, controlled experiments showed that γ-terpinene and light were indispensable in this transformation. The formation and reactivity of the cyclohexadienyl radical **4•** (λ$_{max}$ = 315 nm) were then monitored by laser-flash photolysis measurements. In this study, cyclohexadiene was irradiated at hν = 355 nm with the existence of (ᵗBuO)^2 and various alkyl and aryl halides, leading to the decay of **4•** with similar bimolecular rate constants (k2 ≈ 105 mol L^{-1} s^{-1}). This kinetic result contrasted with the huge distinction in rates measured for the decays of silicon radicals in the existence of similar quenchers. Further DFT computational analysis showed the aromatization process to form naked H• would get over a high kinetic barrier (>15 kcal mol^{-1}), and this
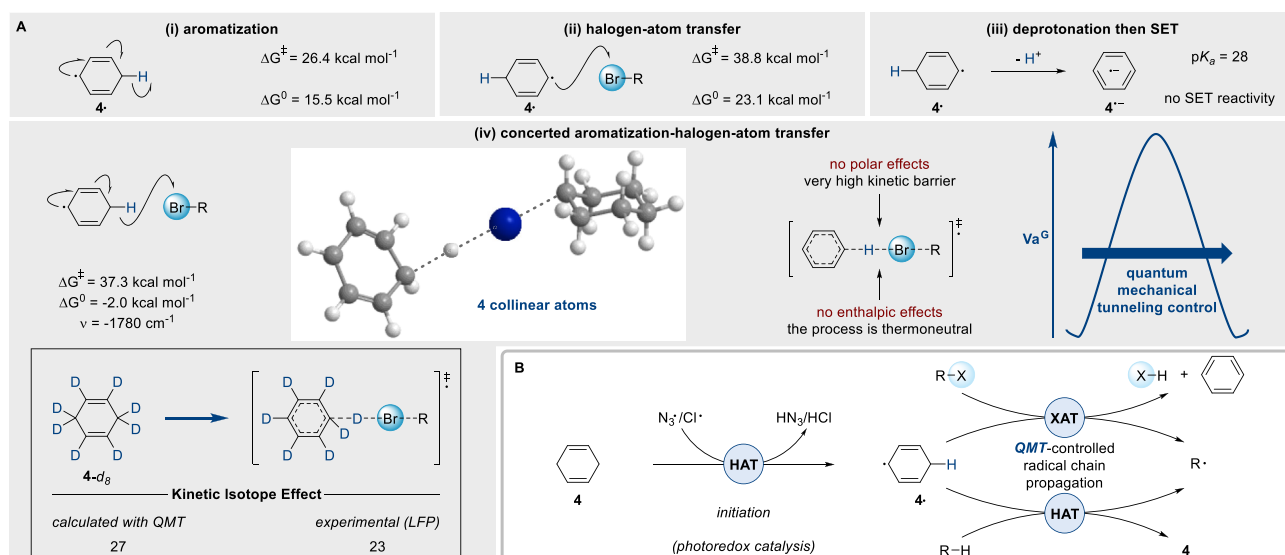
Fig. 2. Mechanism study. (A) Investigation and verification of the quantum-tunneling–promoted concerted aromatization–halogen-atom transfer process. (B) Proposed mechanistic pathway.

would be incompatible with the rapid reactivity investigated under the synthetic reactions (Fig. 2A–i). Moreover, the performed DFT computational calculations would exclude the bromine-atom transfer and group transfer that occurred from 4• due to the highly endergonic and kinetically unfavorable process (Fig. 2A–ii). In the light of the calculated high acid dissociation constant (pK_a = 28) for the methylenic proton in 4•, deprotonation of 4• to the related phenyl radical anion 4•− followed by the SET process of the feedstocks would be also eliminated (Fig. 2A–iii). These results indicated the aromatization and the H•-mediated halogen abstraction were related and took place simultaneously (Fig. 2A–iv). This noncanonical halogen-atom and group transfer chemistry featured a collinear arrangement of four atoms instead of three in the transition state. On the basis of DFT calculations to concerted aromatization-halogen-atom transfer, the bromine abstraction between 4• and 1 was closely approximate to thermoneutrality (ΔG0 = −2.0 kcal mol^{-1}; where ΔG0 is Gibbs free energy; ΔG0 < 0 represents exergonic process and thermodynamic favorableness), but in which an extremely high kinetic barrier (ΔG‡ = 37.3 kcal mol^{-1}; where ΔG‡ is Gibbs energy of activation; ΔG‡ > 0 represents kinetic resistance) was possessed and lead to inhibition of the reactivity. Whereas, the greatly large imaginary frequency monitored (ν = 1780 cm^{-1}) meant a barrier with a quite narrow width [7]. These implied the H atom, as a light particle, is not strictly required to have sufficient kinetic energy to surmount the height of the transition state but can overcome the potential energy barrier via quantum mechanical tunneling (QMT) [2–4]. Experimentally, the large measured (KIE = 23) and calculated (KIE = 27) kinetic isotope effects (KIEs) of fully deuterated cyclohexadienyl radical 4-d8 in the model bromine abstraction approach further validated the QMT process that occurred in this transformation.

Mechanically, the experimental evidence suggests that this γ-terpinene–based strategy might be based on a photoredox-initiated radical chain propagation (Fig. 2B). The SET oxidation of NaCl or NaN$_3$ additives is utilized to approach the corresponding radical Cl• or N$_3$•. The radical propagation would be initiated by these radical intermediates leading to the generation of the cyclohexadienyl species 4• via rapid and favorable H-atom abstraction with the substituted cyclohexadiene [8]. Numerous feedstocks would be converted into the related alkyl and aryl radicals through the quantum mechanical tunneling promoted aromatization–halogen atom transfer. Finally, the radical species could restart the chain by H-atom

transfer (HAT) on 4 or employ first in other types of reactivity, such as cyclization and Giese addition. Furthermore, there are achievement of numerous halogen-atom and group transfer processes (Fig. 1C), while these different types of reactions possessed similar reaction parameters and barrier features. Hence, all the information demonstrates that quantum mechanical tunneling might be a crucial element for the whole class of radical formations.

In conclusion, novel and highly efficient noncanonical halogen-atom and group transfer reactions were implemented by quantum mechanical tunneling (QMT), which could challenge thermodynamic and kinetic control. These transformations also possessed high function group compatibilities and potential values in pharmaceutical syntheses.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Fen-Er Chen is an editorial board member/editor-in-chief for Green Synthesis and Catalysis and was not involved in the editorial review or the decision to publish this article.

Acknowledgments

References

[1] C. Chatgilialoglu, C. Ferreri, Y. Landais, V.I. Timokhin, Chem. Rev. 118 (2018) 6516–6572.
[2] J. Meisner, J. Kästner, Angew. Chem. Int. Ed. 55 (2016) 5400–5413.
[3] P.R. Schreiner, J. Am. Chem. Soc. 139 (2017) 15276–15283.
[4] P.R. Schreiner, Trends Chem. 2 (2020) 980–989.
[5] A. Bhunia, A. Studer, Chem 7 (2021) 2060–2100.
[6] T. Constantin, B. Górski, M.J. Tilby, S. Chelli, F. Juliá, J. Llaveria, K.J. Gillen, H. Zipse, S. Lakhdar, D. Leonori, Science 377 (2022) 1323–1328.
[7] P.R. Schreiner, H.P. Reisenauer, D. Ley, D. Gerbig, C.-H. Wu, W.D. Allen, Science 332 (2011) 1300–1303.
[8] B. Schweitzer-Chaput, M.A. Horwitz, E. de Pedro Beato, P. Melchiorre, Nat. Chem. 11 (2019) 129–135.