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Theoretical Study of C—H bond Cleavage via Concerted Proton-Coupled Electron Transfer in Fluorenyl-Benzoates

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Abstract

Developing new strategies to activate and cleave C—H bonds is important for a broad range of applications. Recently a new approach for C—H bond activation using multi-site concerted proton-coupled electron transfer (PCET) involving intermolecular electron transfer to an oxidant coupled to intramolecular proton transfer was reported. For a series of oxidants reacting with 2-(9H-fluoren-9-yl)benzoate, experimental studies revealed an atypical Brønsted α , defined as the slope of the logarithm of the PCET rate constant versus the logarithm of the equilibrium constant or the scaled driving force. Herein this reaction is modeled with a vibronically nonadiabatic PCET theory. Hydrogen tunneling, thermal sampling of the proton donor-acceptor mode, solute and solvent reorganization, and contributions from excited states are found to play important roles. The calculations qualitatively reproduce the experimental observation of a Brønsted α significantly less than 0.5 and explain this shallow slope in terms of exoergic processes between pairs of electron-proton vibronic states. These fundamental mechanistic insights may guide the design of more effective strategies for C—H bond activation and cleavage.

Graphical Abstract

The activation and cleavage of C—H bonds is an important frontier in synthetic chemistry with a wide range of industrial applications. This process is particularly challenging because of the low polarity and high bond dissociation energy of C—H bonds. Typical mechanisms of C—H activation include oxidative addition, sigma bond metathesis, 1,2 addition, electrophilic activation, and metal-radical activation.^{1,2} Recently a new strategy for C—H bond activation³

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Computational details and supplementary tables and figures.

using multi-site concerted proton-coupled electron transfer (PCET)^{4–15} was proposed. This C–H bond cleavage mechanism involves intermolecular electron transfer to an oxidant coupled to intramolecular proton transfer to a well-positioned proton acceptor.

This strategy for C–H bond activation was demonstrated for 2-(9H-fluoren-9-yl)benzoate, in which the benzylic C–H bond and the carboxylate group are positioned in a manner that facilitates proton transfer from the carbon to the oxygen (Figure 1). The C–H bond cleavage reaction was carried out in acetonitrile using a range of ferrocenium (FeCp_2^+) and aminium (NAr_3^{*+}) oxidants.³ Experimental data indicate that the electron and proton transfer to different sites with no stable intermediates. An approximately linear correlation between the logarithm of the reaction rate constant, $\log(k_{\text{PCET}})$, and the logarithm of the equilibrium constant, $\log(K_{\text{eq}})$, (i.e., the scaled thermodynamic driving force) was reported.³ Interestingly, the slope, or the Brønsted α , of 0.21 ± 0.01 obtained for this reaction was significantly lower than the value of ~ 0.5 typically observed for hydrogen atom transfer reactions of C–H bonds¹⁶ and PCET reactions at polar O–H or N–H bonds.^{5,11–12} The H/D kinetic isotope effects (KIEs) with deuterium selectively substituted at the 9-position of the fluorene ranged from 1.6 to ~ 4.5 for the series of oxidants.

Herein we perform theoretical calculations of this PCET reaction to obtain mechanistic insights and explain the unusually low experimental value of the Brønsted α . These calculations are based on vibronically nonadiabatic PCET theory,^{6,17–20} which is an extension of Marcus theory for electron transfer. In this theory, the transferring proton as well as the electrons are treated quantum mechanically, and the reaction is described in terms of nonadiabatic transitions between reactant and product electron-proton vibronic states. These vibronic states are represented by two sets of stacked parabolic free energy curves along a collective solvent coordinate, corresponding to the different proton vibrational states for the reactant and product electronic states. According to this theory, reorganization of the solute and solvent leads to a degeneracy of two vibronic states, enabling simultaneous tunneling of the electron and proton from their respective donors to their respective acceptors.

The PCET rate constant at each proton donor-acceptor distance R (i.e., C–O distance) is computed by summing over all pairs of reactant and product vibronic states:^{17,18}

$$k(R) = \frac{1}{\hbar} \sqrt{\frac{\pi}{k_B T \lambda}} \sum_{\mu, \nu} P_{\mu} |S_{\mu\nu}(R) V^{\text{el}}|^2 \exp\left(-\frac{\Delta G_{\mu\nu}^{\ddagger}}{k_B T}\right). \quad (1)$$

Here μ and ν denote the reactant and product electronproton vibronic states, respectively, P_{μ} is the Boltzmann population of the reactant vibronic state μ , $S_{\mu\nu}(R)$ is the overlap integral between the reactant and product proton vibrational wavefunctions μ and ν , λ is the reorganization energy, V^{el} is the electronic coupling, and $\Delta G_{\mu\nu}^{\ddagger}$ is the free energy barrier for the reactant and product vibronic state pair (μ , ν):

$$\Delta G_{\mu\nu}^{\ddagger} = \frac{(\Delta G_{\mu\nu}^0 + \lambda)^2}{4\lambda}, \quad (2)$$

where $\Delta G_{\mu\nu}^0$ denotes the reaction free energy for vibronic state pair (μ, ν) . The total rate constant k_{PCET} is obtained by calculating the rate constants $k(\mu, \nu)$ for a range of proton donor-acceptor distances $k(R)$ and integrating over R , weighting each value by the probability distribution function $P(R)$:

$$k_{PCET} = \int_0^{\infty} k(R)P(R)dR. \quad (3)$$

To compute the input quantities, the 2-(9H-fluoren-9-yl)benzoate system was studied in its anionic and neutral states, corresponding to the reactant and product, respectively (Figures 1 and 2). The oxidant was not included in these calculations, but its effect was incorporated by varying the driving force G^0 . For dexamethylferrocenium, $\text{FeCp}^*{}_2^+$, the reaction free energy was estimated to be $G^0(\text{FeCp}^*{}_2^+) \approx -1.4$ kcal/mol based on effective bond dissociation free energies.³ The calculations described herein were performed with unrestricted density functional theory (DFT) using the B3LYP^{21–22} functional and the 6–31++G** basis set^{23–25} in Gaussian 09.²⁶ Solvent effects were included using a conductor-like polarizable continuum model.^{27–28} Additional computational details are provided in the SI.

The reorganization energy was computed as the sum of the inner-sphere reorganization energy λ_i associated with the solute and oxidant and the outer-sphere reorganization energy λ_s associated with the solvent. The inner-sphere reorganization energies^{20,29} of 2-(9H-fluoren-9-yl)benzoate, $\text{FeCp}^*{}_2^+$, and $\text{N}(\text{ArOMe})_3^{\bullet+}$ were calculated to be 28.4 kcal/mol, 0.18 kcal/mol, and 2.58 kcal/mol, respectively. The large inner-sphere contribution for 2-(9H-fluoren-9-yl)benzoate is ascribed to the difference in hybridization of the donor carbon in the reactant (sp^3) and product (sp^2). The solvent reorganization energy³⁰ was calculated to be 21.4 and 18.8 kcal/mol for $\text{FeCp}^*{}_2^+$ and $\text{N}(\text{ArOMe})_3^{\bullet+}$, respectively. Thus, the total reorganization energies are 49.98 kcal/mol for $\text{FeCp}^*{}_2^+$ and 49.78 kcal/mol for $\text{N}(\text{ArOMe})_3^{\bullet+}$. These values were assumed to be the same for all oxidants of each type. Since our calculations show that the Brønsted α does not depend significantly on the reorganization energy within a wide physically reasonable range (Figure S5), these estimates do not impact the analysis or conclusions of this study. The electronic coupling corresponding to electron transfer from the fluorenyl-benzoate to the external oxidant is assumed to be independent of R and to be the same for all oxidants in this study.

As the PCET rate constant must be computed for a series of R values, we performed a series of constrained reactant and product geometry optimizations in which the C–O distance was constrained to specified values. The resulting electronic energies of the reactant state were used to compute the probability distribution function $P(R)$. Moreover, for each value of R ,

we obtained an average geometry in between the optimized reactant and product geometries, approximately corresponding to the crossing point along an inner-sphere solute coordinate. For each of these average structures, we computed a one-dimensional proton potential energy curve for the reactant (anionic) and product (neutral) states. The proton vibrational wavefunctions and energy levels, as well as the overlap integrals, were computed numerically for each of these proton potentials.

These input quantities were used to calculate the total PCET rate constant for the series of oxidants. Note that the second-order rate constant is the product of the equilibrium constant for the formation of a reactive complex between the fluorenyl-benzoate and the oxidant and the first-order PCET rate constant within this complex. This equilibrium constant does not impact the relative rate constants, assuming it is the same for all oxidants. The resulting plot of $\log k_{PCET}$ versus the scaled G^0 is approximately linear with a slope of 0.37, higher than the experimentally determined value of 0.21. However, both of these slopes are below the typical Brønsted α value of ~0.5 for PCET reactions involving the cleavage of C–H bonds¹⁶ or polar O–H and N–H bonds.^{5,11–12} The relatively shallow slope can be explained by analyzing the Brønsted slope for a given pair of vibronic states (μ, ν) in Eq. 1:

$$\frac{d\log k_{\mu\nu}}{d\log K_{\mu\nu}} = 0.5 + \frac{\Delta G_{\mu\nu}^0}{2\lambda}, \quad (4)$$

where $\log K_{\mu\nu} = -\Delta G_{\mu\nu}^0/(2.303RT)$. According to our analysis, $\Delta G_{\mu\nu}^0$ is negative for all pairs of vibronic states contributing significantly to the PCET rate constant for the range of driving forces studied (Tables S9, S10). Summing over all pairs of vibronic states leads to an overall slope below 0.5. The calculated KIEs range from 3.1 to 8.1, which are slightly higher than the experimental values.

Our calculations provide an explanation for the relatively shallow slope (Figure 3) and insight into the mechanism for this C–H bond activation and cleavage reaction. Although the equilibrium proton donor-acceptor distance R (i.e., the distance between the carbon and the oxygen) is 3.0 Å for both reactant and product, evaluation of the integrand in Eq.3 indicates that the dominant R is 2.65 Å because the rate constant increases significantly as R decreases (Figure S3). Moreover, our calculations indicate that the excited reactant and product vibronic states contribute significantly to this reaction (Tables S9, S12 and Figures S5, S6). These contributions are determined by a balance among the Boltzmann population of the reactant state, the free energy barrier, and the overlap between the reactant and product proton vibrational wavefunctions.^{8–10} Typically, the overlap is larger for moderately excited proton vibrational states because they are more delocalized (Figure S7).

Figure 4 depicts the parabolic free energy curves along the collective solvent coordinate, as well as the proton potential energy curves along the proton coordinate and the associated proton vibrational wavefunctions at the dominant proton donor-acceptor distance. For low driving forces, the dominant pairs of states are the ground and first three excited reactant states transitioning to the ground product state. Although the Boltzmann population always

favors the ground reactant state, the excited reactant states contribute because the activation free energy barriers are lower and the overlap integrals are larger for these excited states (Table S9). For higher driving forces, the dominant pairs of states are the ground reactant state transitioning to the ground and first three excited product states. Although the free energy barrier from the ground reactant state is lowest for the ground product state, the overlaps are larger for the excited product states (Table S10). Similar behavior is observed for larger proton donor-acceptor distances, but at these distances the contributions from higher excited states are greater (Tables S11, S12).

The quantitative difference between the calculated and experimentally measured slopes, as well as the KIEs, is most likely due to the challenges associated with applying the PCET theory for this system. In particular, the reactant and product states exhibit large structural differences, and the proton transfer pathway does not appear to be collinear with the proton donor-acceptor axis. Consequently, the use of an average structure and one-dimensional proton potential energy curves to obtain the proton vibrational wavefunctions and energy levels is expected to introduce quantitative error. Nevertheless, the qualitative mechanism, which involves significant contributions from excited vibronic states and simultaneous tunneling of the electron and proton, as well as the explanation for the shallow slope in terms of the dominant exoergic terms in the rate constant expression, is independent of these details.

Herein we presented a theoretical study of C–H bond activation and cleavage via multi-site concerted PCET involving intermolecular electron transfer from a fluorenyl-benzoate to an oxidant and intramolecular proton transfer from the carbon to a well-positioned carboxylate group. Our study indicates that the experimental results can be reproduced qualitatively with a PCET model in which reorganization of the solute and solvent enables simultaneous electron and proton tunneling, with significant contributions from excited electron-proton vibronic states. The relatively shallow slope with the Brønsted α less than 0.5 can be explained in terms of the negative reaction free energies associated with the dominant pairs of vibronic states. These fundamental mechanistic insights may have broader implications for strategies targeting more effective C–H bond activation and cleavage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Hartwig JF Evolution of C–H bond functionalization from methane to methodology. *J. Am. Chem. Soc* 2016, 138, 2–24. [PubMed: 26566092]
2. Labinger JA; Bercaw JE Understanding and exploiting C–H bond activation. *Nature* 2002, 417, 507–514. [PubMed: 12037558]

3. Markle TF; Darcy JW; Mayer JM A new strategy to efficiently cleave and form C–H bonds using proton-coupled electron-transfer. *Sci. Adv.* 2018, 4, eaat5776. [PubMed: 30027119]
4. Stubbe J; Nocera DG; Yee CS; Chang MCY Radical Initiation in the Class I Ribonucleotide Reductase: Long-Range Proton-Coupled Electron Transfer? *Chem. Rev* 2003, 103, 2167–2202. [PubMed: 12797828]
5. Markle TF; Rhile IJ; DiPasquale AG, Mayer JM Probing concerted proton–electron transfer in phenol–imidazoles. *Proc. Natl. Acad. Sci. U.S.A* 2008, 105, 8185–8190. [PubMed: 18212121]
6. Hammes-Schiffer S; Soudackov AV Proton-coupled electron transfer in solution, proteins, and electrochemistry. *J. Phys. Chem. B* 2008, 112, 14108–14123. [PubMed: 18842015]
7. Dempsey JL, Winkler JR, Gray HB, Proton-coupled electron flow in protein redox machines. *Chem. Rev* 2010, 110, 7024–7039. [PubMed: 21082865]
8. Weinberg DR; Gagliardi CJ; Hull JF; Murphy CF; Kent CA; Westlake BC; Paul A; Ess DH; McCafferty DG; Meyer TJ. Proton-coupled electron transfer. *Chem. Rev* 2012, 112, 4016–4093. [PubMed: 22702235]
9. Hammes-Schiffer S Proton-coupled electron transfer: Moving together and charging forward. *J. Am. Chem. Soc* 2015, 137, 8860–8871 [PubMed: 26110700]
10. Bourrez M; Steinmetz R; Ott S; Gloaguen F; Hammarström L Concerted proton-coupled electron transfer from a metal-hydride complex. *Nat. Chem* 2015, 7, 140–145.
11. Miller DC; Tarantino KT; Knowles RR Proton-coupled electron transfer in organic synthesis: Fundamentals, applications, and opportunities. *Top. Curr. Chem* 2016, 374, 30.
12. Morris WD; Mayer JM Separating proton and electron transfer effects in three-component concerted proton-coupled electron transfer reactions. *J. Am. Chem. Soc* 2017, 139, 10312–10319 [PubMed: 28671470]
13. Klinman JP; Offenbacher AR; Hu S Origins of Enzyme Catalysis: Experimental Findings for C–H Activation, New Models, and Their Relevance to Prevailing Theoretical Constructs. *J. Am. Chem. Soc* 2017, 139, 18409–18427. [PubMed: 29244501]
14. Huynh MT; Mora SJ; Villalba M; Tejada-Ferrari ME; Liddell PA; Cherry BR; Teillout A-L; Machan CW; Kubiak CP; Gust D; Moore TA; Hammes-Schiffer S and Moore AL Concerted one-electron two-proton transfer processes in models inspired by the Tyr-His couple of photosystem II. *ACS Cent. Sci* 2017, 3, 372–380. [PubMed: 28573198]
15. Liu T, Guo M, Orthaber A, Lomoth R, Lundberg M, Ott S, & Hammarström L Accelerating proton-coupled electron transfer of metal hydrides in catalyst model reactions. *Nat. Chem* 2018, 10, 881–887. [PubMed: 30013192]
16. Mayer JM Hydrogen atom abstraction by metal–oxo complexes: Understanding the analogy with organic radical reactions. *Acc. Chem. Res* 1998, 31, 441–450.
17. Soudackov A; Hammes-Schiffer S Derivation of rate expressions for nonadiabatic proton-coupled electron transfer reactions in solution. *J. Chem. Phys* 2000, 113, 2385–2396.
18. Soudackov A; Hatcher E and Hammes-Schiffer S Quantum and dynamical effects of proton donor-acceptor vibrational motion in nonadiabatic proton-coupled electron transfer reactions. *J. Chem. Phys* 2005, 122, 014505.
19. Hammes-Schiffer S; Stuchebrukhov AA Theory of coupled electron and proton transfer reactions. *Chem. Rev* 2010, 110, 6939–6960. [PubMed: 21049940]
20. Auer B; Fernandez LE; Hammes-Schiffer S Theoretical analysis of proton relays in electrochemical proton-coupled electron transfer. *J. Am. Chem. Soc* 2011, 133, 8282–8292. [PubMed: 21524104]
21. Becke AD, Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* 1993, 98, 5648–5652.
22. Lee C; Yang W; Parr RG, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B Condens. Matter* 1988, 37, 785–789. [PubMed: 9944570]
23. Hehre WJ, Ditchfield R; Pople JA Self-Consistent Molecular Orbital Methods. 12. Further extensions of Gaussian-type basis sets for use in molecular-orbital studies of organic-molecules. *J. Chem. Phys* 1972, 56, 2257.

24. Clark T; Chandrasekhar J; Spitznagel GW; Schleyer P v. R. Efficient diffuse function-augmented basis-sets for anion calculations. 3. The 3–21+G basis set for 1st-row elements, Li-F. *J. Comp. Chem* 1983, 4, 294–301.
25. Hariharan PC; Pople JA Influence of polarization functions on molecular-orbital hydrogenation energies. *Theor. Chem. Acc* 1973, 28, 213–22.
26. Frisch MJ; Trucks GW; Schlegel HB; Scuseria GE; Robb MA; Cheeseman JR; Scalmani G; Barone V; Petersson GA; Nakatsuji H; Li X; Caricato M; Marenich A; Bloino J; Janesko BG; Gomperts R; Mennucci B; Hratchian HP; Ortiz JV; Izmaylov AF; Sonnenberg JL; Williams-Young D; Ding F; Lipparini F; Egidi F; Goings J; Peng B; Petrone A; Henderson T; Ranasinghe D; Zakrzewski VG; Gao J; Rega N; Zheng G; Liang W; Hada M; Ehara M; Toyota K; Fukuda R; Hasegawa J; Ishida M; Nakajima T; Honda Y; Kitao O; Nakai H; Vreven T; Throssell K; Jr JAM; Peralta JE; Ogliaro F; Bearpark M; Heyd JJ; Brothers E; Kudin KN; Staroverov VN; Keith T; Kobayashi R; Normand J; Raghavachari K; Rendell A; Burant JC; Iyengar SS; Tomasi J; Cossi M; Millam JM; Klene M; Adamo C; Cammi R; Ochterski JW; Martin RL; Morokuma K; Farkas O; Foresman JB; Fox DJ, Gaussian 09 Revision D.01. 2013.
27. Miertuš S; Scrocco E; Tomasi J Electrostatic Interaction of a Solute with a Continuum. A Direct Utilization of ab initio Molecular Potentials for the Prevision of Solvent Effects. *Chem. Phys* 1981, 55, 117–29.
28. Tomasi J; Mennucci B; Cammi R Quantum mechanical continuum solvation models. *Chem. Rev* 2005, 105, 2999–3093. [PubMed: 16092826]
29. Nelsen SF; Blackstock SC; Kim Y Estimation of inner shell marcus terms for amino nitrogen compounds by molecular orbital calculations. *J. Am. Chem. Soc* 1987, 109, 677–682.
30. Marcus RA On the theory of oxidation-reduction reactions involving electron transfer I. *J. Chem. Phys* 1956, 24, 966–978.

FIGURE 1.

Oxidation of the 2-(9H-fluoren-9-yl)benzoate is accompanied by C–H bond cleavage via multi-site concerted PCET, leading to the radical product. The calculations herein focus on this PCET step, but experimentally this radical is found to rapidly undergo oxidative deprotonation and cyclization to form a lactone.

FIGURE 2.
Equilibrium geometries for the reactant and product computed with DFT.

FIGURE 3.

Computed (red) and experimental (blue) correlations between the logarithm of the PCET rate constant and the logarithm of the equilibrium constant or the scaled driving force. Here $\log K = -\Delta G^0/(2.303RT)$, and $\log K$ uses $\log K$ for $\text{FeCp}^*_2^+$ with $\Delta G^0 = -1.4$ kcal/mol as a reference. The slopes of the linear fits are given for both experimental and calculated data. For comparison the typical slope of 0.5 is shown with a gray dashed line.

FIGURE 4.

Schematic representation of the main contributions to the rate constant for low (A) and higher (B) driving forces. The parabolic free energy surfaces of the reactant (blue) and product (red) electron-proton vibronic states along the collective solvent coordinate are schematic, but the associated proton potential energy curves and vibrational wavefunctions are from the calculations at the dominant R of 2.65 Å. For low driving forces, the dominant contributions arise from the lowest four reactant and ground product states, while for higher driving forces the dominant contributions arise from the ground reactant and lowest four product states.