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Lone Pair−π and π−π Interactions Play an Important Role in Proton-Coupled Electron Transfer Reactions

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Abstract: Proton-coupled electron transfer (PCET), a class of formal hydrogen atom transfer (HAT) reactions, is of widespread interest because it is implicated in a broad range of chemical and biochemical processes. PCET is typically differentiated from HAT by the fact that it occurs when a proton and electron are transferred between different sets of molecular orbitals. Previous theoretical work predicted that hydrogen bonding between reactants is a necessary but not sufficient condition for H exchanges to take place by PCET. This implies that HAT is the only mechanism for H exchange between two carbon atoms. In this work, we present computational results that show that the H exchange in the *tert*-butylperoxyl/phenol couple, a prototypical antioxidant exchange reaction, occurs by PCET and that the transfer of the electron can occur via an oxygen lone pair−ring π overlap. We then show that the H exchange in a model for the tyrosyl/tyrosine couple, which is implicated in ribonucleotide reductase chemistry, occurs via PCET and that one path for the electron transfer is provided by a strong π-stacking interaction. Finally, we show that a π-stacking interaction in the benzyl/toluene couple, a system in which there is no H-bonding, can result in this exchange occurring via PCET to some extent. Collectively, these results indicate that PCET reactions are not unique to systems that can engage in H-bonding and that lone pair−π and π−π interactions in these systems may be more important than previously understood.

Introduction

Proton-coupled electron transfer (PCET), a class of formal hydrogen atom transfer (HAT) reactions, is of widespread interest because it is implicated in a broad range of chemical and biochemical processes.[1−3] As recently described in an excellent work by Mayer and Borden et al., PCET is differentiated from HAT by the fact that it occurs when a proton and an electron are transferred between different sets of molecular orbitals.[4,5] The PCET mechanism is illustrated in Figure 1a for the phenoxyl/phenol couple. The phenoxyl radical has its unpaired electron in a singly occupied molecular orbital (SOMO) that is orthogonal to the molecular framework and has two lone pairs of electrons in the molecular plane localized on the oxygen
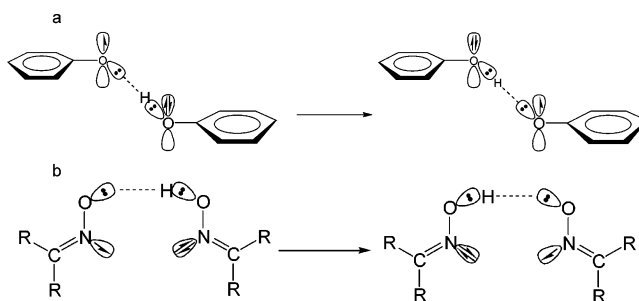

Figure 1. (a) Schematic showing the phenoxyl/phenol PCET mechanism for H atom exchange. Proton transfer occurs between O lone-pair σ-type orbitals that are nominally in the plane of the molecular framework. Electron transfer between O p-type orbitals that are orthogonal to the molecular framework accompanies the proton transfer. (b) Schematic showing the iminoxyl/oxime five-center, cyclic PCET mechanism for H atom exchange. Proton transfer occurs between O lone-pair σ-type orbitals. Electron transfer occurs between the N lone-pair σ-orbitals. For both examples, only the relevant orbitals are illustrated.

atom. Prior to hydrogen atom transfer from phenol to phenoxyl, the couple will form a pre-reaction hydrogen-bonded (H-bonded) complex involving the −OH group of the phenol and one of the O lone pairs on the phenoxyl. The complex is nearly planar and is predicted to lie 9.9 kcal/mol lower in energy than the separated reactants.[4] The H exchange reaction has a nearly planar transition state (TS) that is calculated to be lower in energy than the separated reactants by 1.3 kcal/mol. The H transfer involves three atomic centers and occurs through the migration of the phenol proton across the H-bond to an O lone

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(5) It is important to point out that, for cases where the proton and electron are transferred to the same center, there is no available experimental approach that can be used to differentiate between the HAT and PCET mechanisms. In this connection, Skone et al.[6] have argued that a rigorous distinction between the two mechanisms is not possible because the proton and electron behave quantum mechanically.

(6) Skone, J. H.; Soudackov, A. V.; Hammes-Schiffer, S. *J. Am. Chem. Soc.* **2006**, *128*, 16655−16663.

pair. This transfer occurs between σ-orbitals that are nearly in the plane of the molecular framework of the TS complex. Accompanying the proton transfer is the transfer of an electron from a nominally orthogonal lone pair on the phenol oxygen to the SOMO on the phenoxyl radical. The electron transfer occurs in the same direction as the proton transfer. The HAT mechanism for H exchange requires breaking the H-bond between the phenol and the phenoxyl and redirecting the phenol −OH group toward the singly occupied O 2p π-orbital of phenoxyl. In this arrangement, the proton and electron are transferred together between the same sets of orbitals, and the overall process is energetically less favorable than H exchange by the PCET mechanism.

The iminoxyl/oxime identity reaction[7] is another example of a H transfer reaction that occurs by the PCET mechanism. The iminoxyl radical has its unpaired electron localized in the molecular plane, with roughly half the spin density residing on the N atom.[8] A nearly planar H-bonded pre-reaction complex forms between the −OH group of the oxime and the putative in-plane O lone pair of electrons of the iminoxyl radical. Unlike in the phenol/phenoxyl couple, the H transfer that occurs in the iminoxyl/oxime couple occurs via a five-center, cyclic PCET (see Figure 1b). In this exchange, the proton is transferred across the H-bond, between oxygen lone-pair orbitals, while an electron is transferred in the same direction between N orbitals that are in the plane of the molecular framework.

The previous theoretical work of Mayer et al. predicted that H-bonding between reactants[9] is a necessary but not sufficient condition for H exchanges to take place by PCET.[3] This implies that HAT is the only mechanism for H exchange between, for example, two carbon atoms that cannot engage in H-bonding. Here we present computational results that show that the H exchange in the *tert*-butylperoxyl/phenol couple, a prototypical antioxidant exchange reaction, occurs by PCET and that the transfer of the electron can occur via an O lone pair−ring π overlap. We then show that the H exchange in a model for the tyrosyl/tyrosine couple, which is implicated in ribonucleotide reductase (RNR) chemistry, occurs via PCET and that one path for the electron transfer is provided by a strong π-stacking interaction. Finally, we show that a π-stacking interaction in the benzyl/toluene couple, a system in which there is no H-bonding, can result in this exchange occurring via PCET. These results indicate that PCET reactions are not unique to systems that can engage in H-bonding and that lone pair−π and π−π interactions in these systems may be more important than previously understood.

Computational Methods

Calculations on the *tert*-butylperoxyl/phenol and the tyrosyl/tyrosine couples were performed using UB3LYP[10]/6-311++G-(2d,2p), as implemented in the Gaussian 03 program package.[11] All minimum energy structures were verified as such by

vibrational analyses. TS structures had one negative vibration mode that connected the reactants to products.

Rate constants for the *tert*-butylperoxyl/phenol H exchange were calculated according to the conventional transition state theory expression,[12] modified for the effects of quantum mechanical tunneling by the term $(1 + h^2|\nu|^2/24R^2T^2)$,[13] and summed over the two possible reaction paths (vide infra):

$$k_{CTST} = \left(1 + \frac{h^2|\nu|^2}{24R^2T^2}\right)\frac{k_BT}{h}\frac{Q_{TS}}{Q_AQ_B}\,e^{-\Delta E_0/RT} \qquad (1)$$

In this expression, $|\nu|$ is the magnitude of the negative frequency associated with the mode that connects reactants and products, h is Planck's constants, R is the ideal gas constant, k_B is Boltzmann's constant, T is temperature, Q is the partition function, and ΔE_0 is the zero-point-corrected electronic energy difference between the TS and the separated reactants, A and B. The activation energy for the *tert*-butylperoxyl/phenol H exchange was extracted from the slope of the plot of $\ln(k_{CTST})$ vs $1/RT$. This plot and associated data are given in the Supporting Information.

For the model used for the tyrosyl/tyrosine reaction, the geometry of the transition state was optimized with the B3LYP functional using a locally dense basis set (LDBS):[14] the region consisting of the phenol/phenoxyl moieties was assigned 6-311++G(2d,2p) basis sets, while the rest of the system (the protein backbone) was assigned 6-31G(d) basis sets. This approach was used to reduce the calculation run time.

Calculations involving the benzyl/toluene couple were performed using the second-order Møller−Plesset (MP2) correlation method. Although this procedure is much more time-consuming than density functional theory methods, a correlated wavefunction approach was necessary because of the importance of dispersion interactions (π-ring stacking) in this system. Optimization and frequency calculations were carried out using 6-311++G(2d,2p) basis sets. Single-point calculations on the MP2/6-311++G(2d,2p) structures were performed at the (RO)CCSD(T)/6-311++G(2d,2p) level using the Molpro[15] package.

The highest- and singly-occupied molecular orbitals were obtained from single-point calculations on the optimized TS structures using restricted open-shell B3LYP with 6-311++G-(2d,2p) basis sets. Quantitative measures of the selected lone pair−π and π−π interactions in these orbitals were calculated using the overlap expressions from Mulliken.[16] A normalized molecular orbital (MO), ϕ, can be expressed as a linear combination of atomic orbitals, $\phi_i = \sum_{s=1}^{b} c_{si}\chi_s$, where the MO is denoted by the index i and the basis functions χ by the index s, b is some finite number of basis functions, and c is the basis function coefficient. To determine the overlap between functional groups A and B that form a subset of the molecular system, values of $S_{AB} = \sum_{s\in A}\sum_{r\in B}c_{si}c_{ri}\langle\chi_s|\chi_r\rangle$ were calculated.[17−19]

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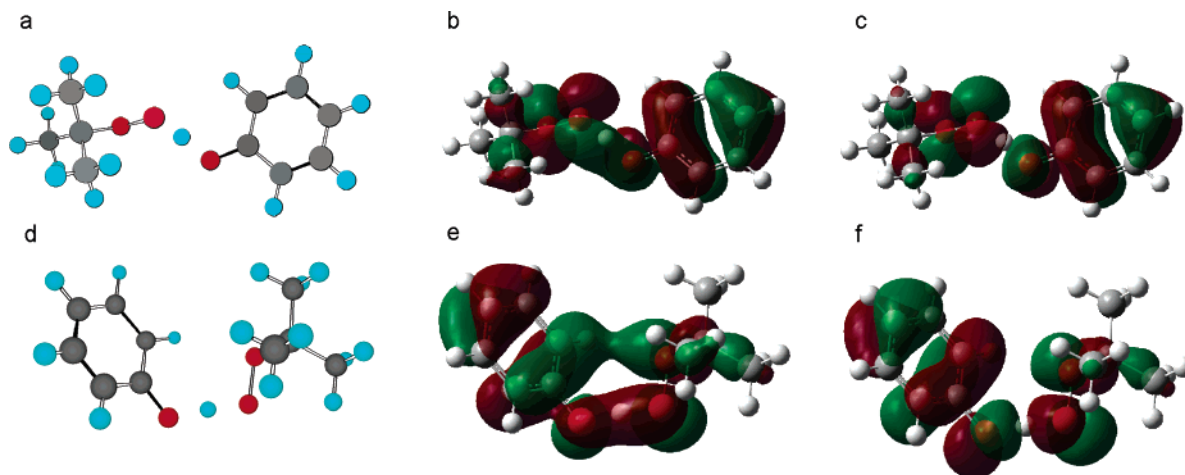(17) O'Boyle, N. M. *GaussSum 2.0*; 2006 (http://gaussum.sf.net).

Figure 2. (a) Structure of the transoid TS of the *tert*-butylperoxyl/phenol couple with the (b) HOMO and (c) SOMO. (d) Structure of the cisoid TS for the *tert*-butylperoxyl/phenol couple with the (e) HOMO and (f) SOMO. The O lone pair−ring π-orbital net bonding overlap in the cisoid TS allows the H exchange to proceed by a multi-center PCET mechanism.

Results and Discussion

We begin with the H exchange in the *tert*-butylperoxyl/phenol couple.[20] This reaction proceeds by two pathways, both of which involve a H-bonded pre-reaction complex. For the higher energy pathway, a pre-reaction complex forms in which the O−O[•] atoms of the *tert*-butylperoxyl are in a transoid arrangement with respect to the phenol C−OH atoms and the calculated H-bond enthalpy is 3.9 kcal/mol. The H-bond involves the phenol O−H group and a lone pair of electrons on the terminal O atom of the *tert*-butylperoxyl radical.

The transoid TS for the *tert*-butylperoxyl/phenol couple has an OO···[H]···OC dihedral angle of 152.8° (Figure 2a) and is computed to lie 5.5 kcal/mol in energy above the separated reactants. The highest-occupied molecular orbital (HOMO, Figure 2b) shows that there is a π-type bonding interaction involving a 2p π atomic orbital of the phenol O atom and the nominally singly occupied 2p atomic orbital of the O atom on *tert*-butylperoxyl. The singly-occupied molecular orbital (SOMO, Figure 2c) displays π-antibonding character across the phenol and *tert*-butylperoxyl O atoms. The π-interaction involving these O atoms is net bonding because the HOMO is doubly occupied and the SOMO is singly occupied. In this transoid TS, proton transfer occurs between O σ-orbitals and the electron transfer occurs via the channel provided by the O−O π-bond. This is characteristic of a three-center PCET reaction, like the phenoxyl/ phenol exchange, where H exchange occurs by moving a proton and an electron between different sets of orbitals on the same atomic centers.[4] A HAT reaction is unlikely to occur in this case because this mechanism requires breaking the pre-reaction complex H-bond and reorienting the phenol to a less favorable arrangement wherein its O−H group is directed toward the nominally singly occupied 2p O[•] orbital in *tert*-butylperoxyl.

The lower energy pathway for the *tert*-butylperoxyl/phenol H exchange involves a cisoid pre-reaction complex which forms from H-bonding between the phenol's O−H group and a lone pair on the *tert*-butylperoxyl's terminal O atom. The computed H-bond enthalpy is 3.9 kcal/mol. The corresponding TS structure (Figure 2d) maintains the cisoid arrangement wherein the OO···[H]···OC dihedral angle is −10.6°. This TS is calculated to be 0.5 kcal/mol lower in energy than the transoid TS despite identical H-bond strengths in the cisoid and transoid pre-reaction complexes.

As is the case in the transoid TS, the HOMO and SOMO (Figure 2e,f) of the cisoid TS structure show that a partially bonding π-orbital forms across the O atoms between which the H is exchanged. Therefore, electron transfer occurs between orbitals other than those involved in proton transfer. However, unlike the transoid TS, the HOMO of the cisoid TS also displays a bonding overlap between a lone pair on the central peroxyl O of the *tert*-butylperoxyl and a delocalized π-orbital on the phenol ring. This interaction arises because the electron-deficient ring[21] can accept electron density from a lone pair on the central oxygen of the *tert*-butylperoxyl and because there is a small distance (3.2 Å) between the C2 of the ring moiety and the central peroxyl O atom. The calculated overlap between the Ph moiety of the phenol and the OtBu (central O) moiety of *tert*-butylperoxyl is 0.01 in the HOMO and −0.02 in the SOMO.

There are two important effects that arise from this interesting lone pair−π overlap in the cisoid *tert*-butylperoxyl/phenol TS. First, the bonding interaction causes the cisoid TS to be lower in energy than the transoid TS. Second, this overlap provides a second channel for electron transfer between the reacting moieties. In the cisoid TS, the proton is transferred between oxygen-centered lone pairs directed along the line connecting the two O centers. At the same time, electron transfer occurs between different sets of orbitals and in the same direction as the proton. The orbitals involved in the electron transfer are a combination of the partially bonding π-orbital involving the central O atoms in the TS structure and the O lone pair−ring π overlap described above. These findings may explain the large

(18) For example, with B3LYP/6-311++G(2d,2p), the overlap population in H_2 at its equilibrium geometry is 0.83 e[−], which gives a dimensionless overlap of 0.21. As a gauge of the magnitude of these values for a PCET transition state, the overlaps between the two N=CH$_2$ groups in the iminoxyl/oxime transition state associated with the reaction illustrated in Figure 1b are 0.05 (HOMO−2) and −0.15 (SOMO), with the negative value indicating an antibonding interaction.

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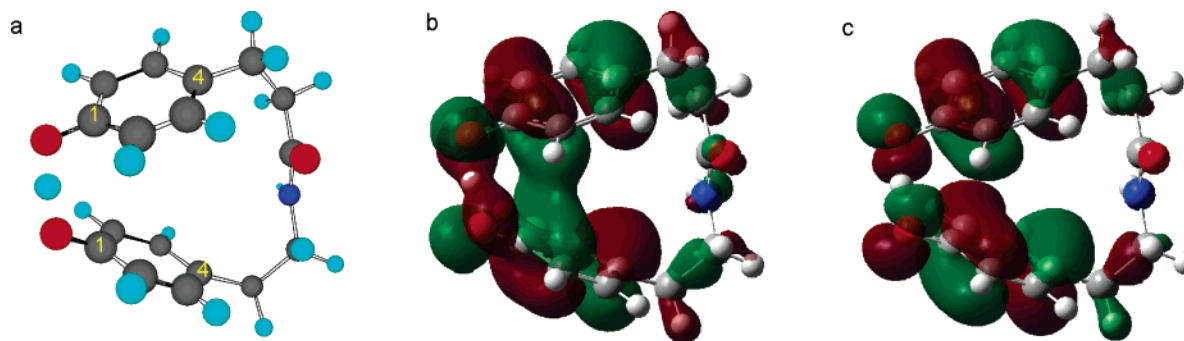
Figure 3. (a) Structure of the TS for the H exchange in the tyrosyl/tyrosine couple (C1 and C4 carbons are indicated with numbers) and the (b) HOMO and (c) SOMO. The ring C1—C1 atoms are separated by 3.2 Å. The $\pi-\pi$ bonding overlap in the TS allows the hydrogen exchange to occur via a multi-center PCET.

rate constant for the *tert*-butylperoxyl/phenol exchange: we obtain a theoretical rate constant (k) of 1.4×10^4 M^{-1} s^{-1} and activation energy (E_a) of 5.6 kcal/mol (relative to separated reactants). These values are in excellent agreement with the experimental results of $k = 2.5 \times 10^3$ M^{-1} s^{-1} and $E_a = 5.2$ kcal/mol.[22]

The interesting involvement of the *tert*-butylperoxyl/phenol couple ring orbitals caused us consider the details of the H exchange in a model of the tyrosyl/tyrosine couple that occurs in RNR.[25] The apparent long-range radical transfer in RNR is, so far as is known, unique in biology. Ongoing work by Nocera and Stubbe[26] aims to understand the nature of this transfer, although others suggest that large conformational changes in RNR are required for the process to take place.[27] Previous theoretical work[25] has focused on the H exchange that occurs in a tyrosyl/tyrosine couple (residues Y731—Y730) in RNR, a process that is one step in the complex, long-range radical transfer. Seigbahn et al. had predicted that the H exchange in the tyrosyl/tyrosine couple occurs by HAT.[25] Our calculated TS structure for this reaction is shown in Figure 3a.

The protein backbone introduces a constraint on the structure of the TS that results in a separation of the phenyl ring C4 atoms of ca. 5 Å. Similarly, the H exchange necessitates the closer approach of the phenolic O atoms in order for the reaction to proceed. These two constraints result in a small separation of only 3.2 Å between the two C1 atoms of the rings in the TS. To transfer the H, the incipient O—H groups rotate 48° and 53° out of their respective ring planes, in agreement with previous work.[25]

Despite the geometric constraints, the HOMO and SOMO of the tyrosyl/tyrosine couple TS (Figure 3b,c) strongly resemble those of the PCET TS of the phenoxyl/phenol couple.[4] However,

because of the small ring separation, there is also a substantial overlap between the π-orbitals of the rings. This is evident in the HOMO (Figure 3b) and from the calculated overlaps of the two Ph moieties in the HOMO (0.03) and the SOMO (−0.07). The H exchange occurs by a proton transfer between lone pairs localized on the O atoms. However, in addition to the concomitant electron transfer between O p-type orbitals, the substantial $\pi-\pi$ overlap allows for electron transfer between the two ring moieties. Therefore, this exchange can be viewed as a PCET reaction involving multiple centers, including the −OH and −O• groups and the ring carbon atoms.

Finally, we present results for the benzyl/toluene couple. This system was also studied in the work of Mayer et al.[4] Previous works predicted that the benzyl/toluene exchange TS structure has C_{2h} symmetry.[4,28] In this arrangement, the rings are as far apart in space as possible, and the transferring H lies along a vector connecting the incipient singly-occupied p-type orbitals of the benzylic C atoms. The SOMO in Mayer et al.'s C_{2h} TS points to a three-center, three-electron interaction between the central C—H—C atoms and supports their conclusion that the benzyl/toluene H exchange occurs via HAT. Subsequent work on this system by Skone et al. indicates that the proton tunnels electronically adiabatically.[6] However, the C_{2h} structure is counter-intuitive because experiment[29] and high-level theory[30] have shown that $\pi-\pi$ dispersion interactions result in benzene dimerization.

We examined the potential energy surface associated with the rotation of the benzyl groups about the CC···[H]···CC dihedral, that is, the rotation that converts the TS structure from C_{2h} to C_{2v} (rings overlapping) symmetry using the MP2 method. This approach is capable of predicting dispersion interactions in the benzene dimer and other van der Waals complexes. Our results indicate that the potential energy minimum lies between the C_{2h} and C_{2v} structures, where the two rings have some overlap. To verify this, we performed full TS optimization calculations at the UMP2/6-311++G(2d,2p) level of theory. These calculations give a TS structure having C_2 symmetry with the benzyl rings oriented at ca. 34° (Figure 4a), 4.0 kcal/mol lower in energy than the C_{2h} structure. The single-point ROCCSD(T)/6-311++G(2d,2p) calculations predicted that the

(22) Recent work by Lingwood et al.[23] showed that the MPW1K[24] method predicts accurate rate constants and barrier heights for certain PCET reactions. For the *tert*-butylperoxyl/phenol couple, MPW1K predicts k_{CTST} = 4.9×10^{-3} M^{-1} s^{-1} and $E_a = 13.1$ kcal/mol (relative to separated reactants). The latter value is in very poor agreement with the experimental E_a, despite the fact that the method was specifically parameterized for hydrogen atom transfer reactions. We attribute this large error to a poor description of the charge separation in the PCET transition state.
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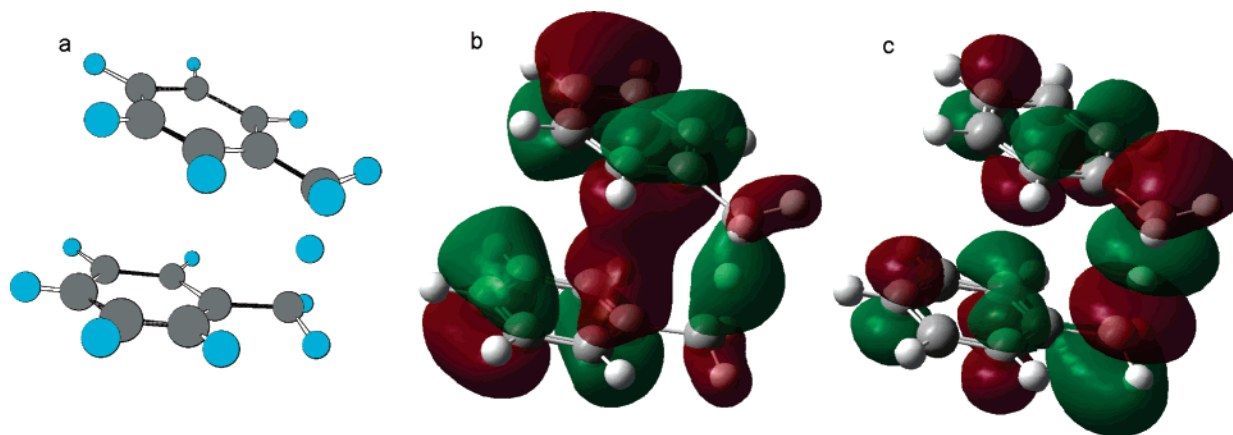
Figure 4. (a) Structure of the TS of the benzyl/toluene couple with the (b) HOMO and (c) SOMO. The overlap between the partially stacked incipient benzyl rings allows for electron transfer between π-systems of the reacting moieties.

energy difference between the lower-lying C_2 TS and the C_{2h} saddle-point[31] is 3.7 kcal/mol.[32,34]

The HOMO and the SOMO for the TS structure are shown in Figure 4b,c. The HOMO shows a σ-bonding interaction between the $-CH_2$ carbon atoms and the transferring H, while the SOMO shows an antibonding interaction between these moieties. In these respects, the HOMO and SOMO for the C_2 TS resemble those reported by Mayer et al.[4] and imply that the reaction occurs by HAT. However, the HOMO also shows a bonding overlap between the rings (Ph–Ph overlaps of 0.02 and −0.01 in the HOMO and SOMO, respectively). This bonding interaction causes the close approach of the rings in the partially stacked TS and allows for electron transfer between the incipient benzyl moieties. Therefore, this reaction can proceed by transferring the proton between the benzylic carbons

(31) The C_{2h} structure has two negative vibration modes at the MP2/6-311++G-(2d,2p) level of theory, indicating that it is a higher-order saddle-point and not a transition state. One negative mode corresponds to the H transfer, and the second mode corresponds to the conversion of the C_{2h} structure to the C_2 structure.

(32) It is well known that the unrestricted MP2 approach can produce unusual results for conjugated open-shell systems like the benzyl radical. Bally and Borden[33] have shown that the UMP2 approach yields a discontinuity in the potential energy profile for the rotation of the benzyl $-CH_2^\bullet$ at ca. 70°. Indeed, our own results show that ring C–C bond lengths obtained with UMP2/6-311++G(2d,2p) are too short by ca. 0.02 Å. However, we expect that the UMP2 approach provides a reasonable treatment of the ring stacking interaction in the benzyl/toluene C_2 TS. This is verified by the ROCCSD(T)/6-311++G(2d,2p) results that show that the C_2 TS is energetically lower-lying than the C_{2h} structure.

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(34) We also performed calculations with dispersion-corrected B3LYP. A rigid potential energy scan about the CC–[H]–CC dihedral was performed with B3LYP/6-311++G(2d,2p) in 5° increments, starting at the optimized C_{2h} geometry. The dispersion energy was obtained at each point on the potential energy surface using the method of Johnson and Becke[35] with parameters $a_1 = 0.52$ and $a_2 = 1.98$ Å. These new parameter values were determined by minimizing the root-mean-square percent error in the binding energies of a test set of seven dispersion-bound hydrocarbon complexes (methane dimer, methane–ethylene, ethylene dimer, methane–benzene, and the parallel, T-shaped, and slipped-parallel conformations of the benzene dimer). This gave an optimum dihedral of ca. 40°, in good agreement with the MP2 results.

(35) Johnson, E. R.; Becke, A. D. *J. Chem. Phys.* **2006**, *124*, 174104.

while an electron is exchanged between rings. The conjugation of the $-CH_2$ groups with the rings ensures that the transferred electron will ultimately localize in a benzyl's $-C^\bullet H_2$ p-orbital. In this case, the mechanism cannot be classified as entirely HAT or PCET. We note that this exchange does not involve a H-bonded pre-reaction complex.

Conclusions

The results of our theoretical calculations show that lone pair–π and π–π overlaps, which are formally nonbonding in the pre-reaction complexes, become partially bonding in TS complexes. In the H exchanges presented in this work, these partial bonding interactions form conduits for electron transfer in the TS and thereby allow the exchanges to occur by PCET to some extent. The findings associated with benzyl/toluene also show that H-bonding in pre-reaction complexes is not a necessary condition for PCET.

These results shed further light on mechanisms of an important class of exchange reactions and reveal that lone pair–π and π–π interactions play a more important role in these reactions than previously understood. These interactions may be found to play a role in radical reactions other than hydrogen atom exchanges.

Supporting Information Available: Complete refs 11 and 15, ln(k) vs 1/T plot for *tert*-butylperoxyl/phenol and associated data, figure of LDBS partitioning in the tyrosyl/tyrosine TS, potential energy curves for the benzyl/toluene couple, and electronic energies and optimized structures for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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