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H-Coupled Electron Transfer in Alkane C−H Activations with Halogen Electrophiles

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Abstract: The mechanisms for the reactions of isobutane and adamantane with polyhalogen electrophiles ($HHal_2^+$, Hal_3^+, Hal_5^+, and Hal_7^+, Hal = Cl, Br, or I) were studied computationally at the MP2 and B3LYP levels of theory with the 6-31G** (C, H, Cl, Br) and 3-21G* (I) basis sets, as well as experimentally for adamantane halogenations in Br_2, Br_2/HBr, and I^+Cl^-/CCl_4. The transition structures for the activation step display almost linear C···H···Hal interactions and are characterized by significant charge transfer to the electrophile; the hydrocarbon moieties resemble the respective radical cation structures. The regiospecificities for polar halogenations of the 3° C−H bonds of adamantane, the high experimental kinetic isotope effects ($k_H/k_D = 3-4$), the rate accelerations in the presence of Lewis and proton (HBr) acids, and the high kinetic orders for halogen (7.5 for Br_2) can only be understood in terms of an H-coupled electron-transfer mechanism. The three centered-two electron (3c-2e) electrophilic mechanistic concept based on the attack of the electrophile on a C−H bond does not apply; electrophilic 3c-2e interactions dominate the C−H activations only with nonoxidizing electrophiles such as carbocations. This was shown by a comparative computational analysis of the electrophilic and H-coupled electron-transfer activation mechanisms for the isobutane reaction with an ambident electrophile, the allyl cation, at the above levels of theory.

Introduction

Functionalizations of alkanes with charged electrophiles E^+ are among the most useful preparative transformations.[1−6] This field was first and foremost developed by George A. Olah, and his many chemical discoveries and contributions have turned into practical solutions for the petroleum industry.[4,5,7−10]

Despite their importance, it is often overlooked that many of these reactions are mechanistically not well understood. Even the term *selective functionalization*, that is, the targeted substitution of a C−H to a C−X bond, is used interchangeably with *selective activation*, although the two do not have to be coupled. To illustrate this point, consider traditional electrophilic alkane chemistry: different starting materials (e.g., *n*-butane and isobutane) may give the same major product.[7] The overall reaction (*functionalization*) *is* selective (predictably giving one product), but the activation does *not* have to be selective (different cationic intermediates may be generated and may be equilibrated rapidly). Very often, this clear-cut distinction is not made, and the terms “activation” and “functionalization” are used interchangeably. The present paper demonstrates that *selective activation* indeed is an important aspect of electrophilic alkane chemistry. In particular, we emphasize the importance of electron-transfer (ET) steps in the reactions of electrophile-oxidizers that are typical also for traditional “electrophilic” alkane activations. We argue, both computationally and experimentally, that the very nature of the intermediate radical cations or radical cationic transition structures is largely responsible for the often observed surprisingly high selectivities in these types of transformations.

A number of strong electrophiles such as the proton,[7] carbocations,[11,12] nitronium salts,[13−18] and positively charged

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halogen reagents[19−21] readily react with alkane C−H and/or C−C bonds. The mechanistic understanding of the activation step, however, is controversial and is based on either the *insertion* of E^+ into the σ-bonds via three centered-two electron (3c-2e) species[8,22,23] or the addition of E^+ by means of direct attack on the atoms.[24]

Experimental mechanistic studies in superacidic media[5,7,25,26] reveal little about the activation step. Mechanistic computational modeling is equally difficult as only intermediates[27−30] rather than transition structures can generally be located for these often highly exothermic reactions. Only a limited number of transition structures for the hydrogen exchange reactions for surface-adsorbed alkanes were found to date.[31−33] Some computations are available for the reactions of alkanes with relatively stable electrophiles such as $H_3O_2^+$,[22] NO^+,[23,24,34] carbocations,[11,12,35,36] and positively charged halogens.[37−39] However, there is no decisive evidence for[22,23] or against[24] an electrophilic 3c-2e activation mechanism, involving the attack on the C−H bonds, that is, via transition structures with triangular C−H−E moieties. In addition, our[17,40,41] and other[42−44] studies on hydrocarbon activations with electrophile-oxidizers show that electron-transfer (ET) processes cannot be ruled out and may actually be dominating. As we pointed out recently,[2] the reactions of electrophiles with alkanes are at the borderline of inner and outer electron transfer,[45] and the hydrocarbon moieties in the transition states or intermediates often resemble radical cation structures. For instance, the lowest-lying transition states for the reactions of methane with NO^+ and BH_2^+ very much resemble the structure of the methane radical cation[46−49] with two elongated C−H bonds (i.e., $[H_2\cdots CH_2-E]^+$) without incorporation of the electrophile in the 3c-2e bonding.[24,49] Methane, however, is not a particularly good model for electrophilic aliphatic substitution mechanistic studies because the triply degenerate HOMO does not describe the individual C−H bonds.[50]

Selective heterolytic (polar) halogenations are characteristic for adamantane,[51] and for a number of other cage hydrocarbons such as diamantane,[52] protoadamantane,[53] 2,4-ethanoadamantane,[54] bicyclo[3.3.1]nonane,[55] as well as for some aliphatic[56,57] compounds. Functionalizations of cage compounds with some other oxidizing electrophiles such as 100% HNO_3[58] and nitrogen-containing electrophiles[15,16,59] are similarly selective. Inter alia, we will provide explanations for the following combined experimental facts observed for polar halogenations of, for example, adamantane: (i) the increase of the reaction rates in the presence of Lewis acids[60] and mixed halogens such as I^+Cl^-,[21] as well as Br^+Cl^-,[61](ii) the high kinetic reaction orders observed for halogen (we have found a reaction order of about 7 for Br_2 in CCl_4), (iii) the observed 100% 3° C−H bond regioselectivities,[51] and (iv) the relatively high experimental H/D kinetic isotope effect (KIE) for the adamantane bromination in Br_2 ($k_H/k_D = 3.9 \pm 0.2$[41]).

The present combination of experiment and theory reveals key aspects of the C−H activation mechanisms of some representative hydrocarbons (methane, isobutane, and adamantane) with a set of model electrophiles ranging from nonoxidizing (i.e., with low electron affinities) carbocations to positively charged halogen oxidizers Hal_n^+. We will show that ET is a prime element for the detailed understanding of the

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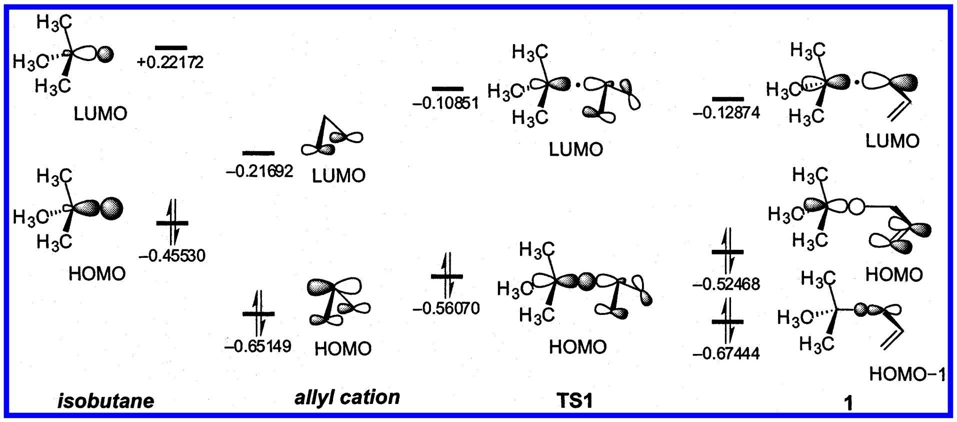


Figure 1. The FMOs of isobutane as well as the allyl cation and the key orbitals for the strongly bonding (**1**) and weakly bonding (**TS1**) interactions of isobutane with the allyl cation (energies in eV, B3LYP/6-31G**).

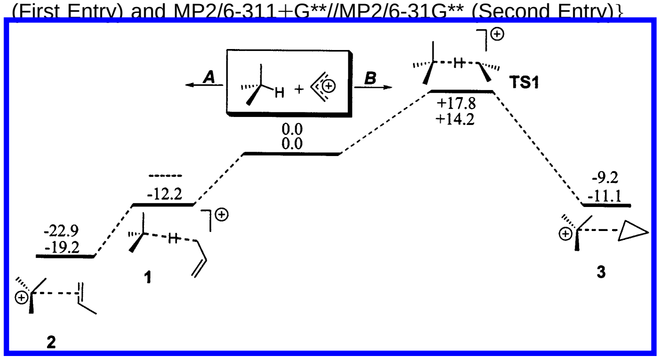
mechanisms of alkane C−H activations with relatively stable (delocalized) electrophiles.

Results and Discussion

Isobutane Reactions with the Allyl Cation. There are a number of indications that hydrogen-transfer reactions of carbocations with alkanes are similar to H-abstractions with radicals.[2,62,63] In many so-called "hydride transfer reactions"[64−66] $R-H + Alk^+ \rightarrow [R\cdots H\cdots Alk]^+ \rightarrow R^+ + H-Alk$, the transferred hydrogen formally does *not* carry a negative charge due to the higher electronegativity of carbon.[2] The VB approach[67] for the simplest model $[H_3C-H-CH_3]^+$ system clearly shows that the hydrogen being transferred indeed has some *radical* character. A detailed MP2 and DFT study[11] on this type of reaction demonstrated that the H-transfer between various alkanes and alkylcarbenium ions proceeds via formation of intermediates with linear or almost linear $[C-H-C]^+$ bonding moieties. An analogous situation was identified[35] for the reactions between silanes and carbenium ions, where ion−molecule clusters with elongated agostic C−H bonds were found by gas-phase computational modeling. We emphasize that only minima were located in the published works; transition structures for the C−H activation of alkanes with carbenium ions have, at least to the best of our knowledge, remained elusive to date.

We found that the *model* reactions of alkanes with the delocalized (and therefore quite stabilized) allyl cation allow us to discern two interaction modes: (A) conventional electrophilic (strongly bonding) and (B) H-coupled ET (weakly bonding). We first studied the reaction of the allyl cation with the 3° C−H bond of isobutane that is characterized by a localized HOMO (i.e., it mostly describes the central C−H bond, Figure 1). The NBO analysis of the allyl cation (C_{2v} symmetry)[68] shows that the positive charge is located mainly on the protons of the terminal CH$_2$ groups. While the C^1 and C^3 atoms are almost uncharged (−0.005e at B3LYP and +0.07e at MP2), the central carbon carries a large negative partial charge (−0.36e at B3LYP and −0.46e at MP2). As a consequence, the charge-controlled interaction must favor an approach of a positively polarized hydrogen atom of the 3° C−H bond to the *central* carbon of the allyl cation. However, the orbital-controlled process involves the LUMO of the allyl cation (Figure 1) and an approach onto the *terminal* carbons of this electrophile. Thus, the interaction of the 3° C−H bond of isobutane with the terminal carbons of the allyl cation represents the strongly bonding (conventional electrophilic) situation, whereas the approach to the central carbon atom of the allyl cation represents the weakly bonding (electron transfer, vide infra) path.

Scheme 1. Strongly Bonding (A) and Weakly Bonding (B) Pathways for the Reaction of Isobutane with the Allyl Cation {Relative ΔG_{298} in kcal/mol at B3LYP/6-311+G**//B3LYP/6-31G** (First Entry) and MP2/6-311+G**//MP2/6-31G** (Second Entry)}



We studied these two activation modes (A and B, Scheme 1) computationally at the B3LYP and MP2 levels of theory. The reaction at a terminal carbon of the allyl cation proceeds through an exothermically formed (MP2, $\Delta_r G_{298} = -12.2$ kcal/mol) tight H-bound complex (**1**, Scheme 1) followed by decomposition to the final complex of the *t*-Bu cation with propene (**2**). In agreement with previous studies on the C−H activations with carbocations, the transition structure for this electrophilic reaction (A) could not be located because of the favorable formation of a three center bonding *minimum*[69] (for the HOMO and HOMO-1 of **1**, see Figure 1). The geometry of the C···H···C moiety of **1** is very similar to that for the complex of the *sec*-propyl cation with isobutane found previously.[11] At B3LYP, only one minimum corresponding to the final complex **2** could be located. The overall electrophilic H-transfer from isobutane to the allyl cation is slightly more exergonic at B3LYP than at MP2 ($\Delta_r G_{298} = -22.9$ vs -19.2 kcal/mol, respectively).

TS1 located along pathway B at B3LYP ($\Delta G^{\ddagger}_{298} = 17.8$ kcal/mol) and MP2 ($\Delta G^{\ddagger}_{298} = 14.2$ kcal/mol) describes the

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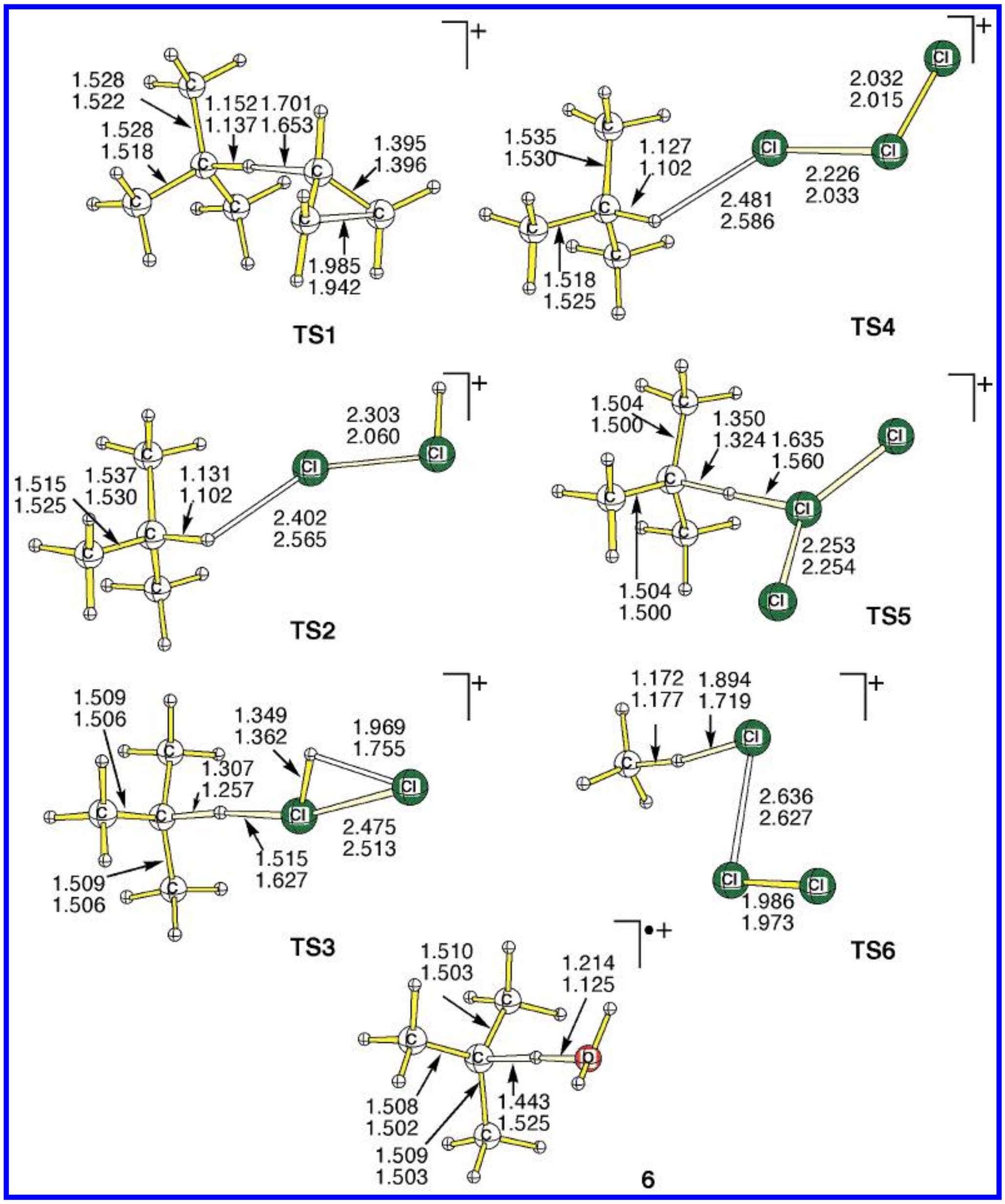

Figure 2. B3LYP/6-31G** (first entry) and MP2/6-31G** (second entry) optimized geometries of **TS1**−**TS6** and the complex of the isobutane radical cation with water (**6**) (bond distances in Å).

H-abstraction from isobutane by the central carbon atom of the allyl cation followed by ring closure to cyclopropane. The IRC procedure from **TS1** terminates with a complex of the *t*-Bu-cation with cyclopropane (**3**). **TS1** is characterized by an only slightly elongated 3° C−H bond (1.152 Å and 1.137 Å at B3LYP and MP2, respectively, Figure 2) with the transition vector describing the linear movement of the transferred hydrogen (about 350*i* cm^{-1} at B3LYP and MP2). Although the distance to the electrophile in **TS1** is relatively long, the charge transfer from isobutane to the allyl cation is substantial (ca. 0.25e from NBO analysis), and the charge on the hydrogen atom transferred is *positive* (+0.15e). This mechanism is clearly different from the A activation mode and shows some common features with radical C−H abstractions: The HOMO of **TS1** (Figure 1) describes the *antibonding* interaction between the electrophile and the C−H bond and is quite similar to the SOMOs of the transition structures for C−H abstractions with radical reagents.[70,71]

Hence, **TS1** represents the weakly bonding situation as a superposition of the $[\mathrm{R}\cdots\mathrm{H}\cdots\mathrm{E}^{+}]$ and $[^{+\bullet}\mathrm{R}\cdots\mathrm{H}\cdots\mathrm{E}^{\bullet}]$ VB-states and resembles the structures of the isobutane (R−H) and trimethylene (H−E) radical cations[72,73] in an averaged $[^{\delta+\bullet}\mathrm{R}\cdots\mathrm{H}\cdots\mathrm{E}^{\delta+\bullet}]$ structure. In an alternative view, and this explains the ET pathway B, the cyclopropane moiety in **TS1** resembles that of its radical cation where one C−C bond is substantially elongated[72,74] (an electron is removed from the respective C−C bonding orbital). This activation mode is an example for an H-coupled ET from the alkane to the electrophile along the C−H activation path. **TS1** falls into the regime of a "hydrogen-coupled electron transfer" where the transferred

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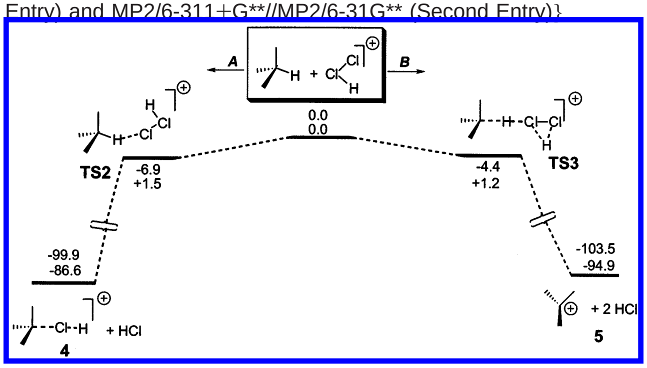
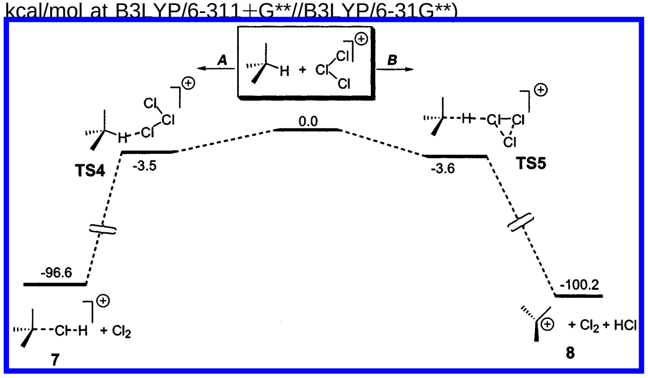
Scheme 2. The Electrophilic (A) and H-Coupled Electron-Transfer (B) C−H Activations of Isobutane with Protonated Chlorine HCl_2^+ {ΔG_{298} in kcal/mol at B3LYP/6-311+G**//B3LYP/6-31G** (First Entry) and MP2/6-311+G**//MP2/6-31G** (Second Entry)}



Scheme 3. The Electrophilic (A) and H-Coupled Electron-Transfer (B) C−H Activations of Isobutane with Cl_3^+ (Relative ΔG_{298} in kcal/mol at B3LYP/6-311+G**//B3LYP/6-31G**)



hydrogen carries only a *small* positive charge in an overall *two*-electron-transfer process. This re-emphasizes the relationship of these types of reactions with radical H-abstractions. Conversely, the traditional inner-sphere proton-coupled ET[75,76] involves transfer of one electron and one proton in an overall *one*-electron-transfer process.

Our theoretical analysis of the reactions of the allyl cation with isobutane reveals two different types of reactions: strongly bonding electrophilic (A) and weakly bonding oxidative (B), that is, inner-sphere electron transfer. The unique nature of **TS1** reveals the role of ET in the electrophilic alkane C−H activation processes. While it is clear that pathway B is energetically less favorable than A for the allyl cation (our exploratory model), we now show that ET is important for alkanes reacting with weakly electrophilic but strongly oxidizing electrophiles such as halogen-containing cationic species.

Isobutane Reactions with HCl_2^+ and Cl_3^+. One of the simplest positively charged halogen singlet ground-state electrophiles, protonated chlorine (HCl_2^+),[77] carries three equally (ca. +0.3e) polarized electrophilic centers.[78] Both chlorine atoms share the HOMO and LUMO coefficients; the contribution of the terminal chlorine atom is slightly higher. Consequently, we found two different transition structures for the H-transfer from isobutane to HCl_2^+ (Scheme 2).[79] The early nonlinear **TS2** formally describes the electrophilic (A) insertion of the terminal chlorine of HCl_2^+ into the C−H bond (Scheme 2). **TS2** is similar to the transition state previously found[22] for the reaction of this hydrocarbon with $H_3O_2^+$: It displays an only slightly elongated 3° C−H bond (1.131 and 1.102 Å at B3LYP and MP2, respectively) and has a negligible ET contribution due to little charge transfer from isobutane to the electrophile (ca. 0.02e). The reaction is barrierless at B3LYP but has a low barrier at MP2 ($\Delta G^{\ddagger}_{298}$ = 1.5 kcal/mol). Initial complexes were located but not included in the energy evaluations at MP2 because their formation is endergonic by ca. +0.2−0.5 kcal/mol. An electron-transfer **TS3** (Scheme 2, pathway B), located at both levels, describes the H-abstraction from isobutane by the central chlorine atom of HCl_2^+ leading to the isobutane cation and two HCl molecules (**5**). The C−H bond in the transition structure is substantially elongated (1.307 Å and 1.257 Å at B3LYP and MP2, respectively), and significant charge transfer (ca. 0.6e) from the hydrocarbon to HCl_2^+ is indicated. The **TS3** orbitals are similar to those of **TS1**; that is, the HOMO describes the antibonding interactions between the 3° C−H bond hydrogen and the electrophile. Note that the charge transfer in **TS3** is substantially higher than that in **TS1**; the H-coupled ET from isobutane to the strong oxidant HCl_2^+ dominates.

The two pathways (A and B) for the reaction of isobutane with HCl_2^+ have comparable barriers (1.5 vs 1.2 kcal/mol at MP2, respectively), but the electrophilic mechanism is thermodynamically slightly more favorable (−4.4 vs −6.9 kcal/mol at B3LYP).

For another simple model electrophile Cl_3^+ (Scheme 3) which serves as a source of "Cl^+" in C−H functionalizations,[39] pathway B via **TS5** is marginally more favorable (Scheme 3). Because of the system size, the frequencies could only be computed at DFT, but the MP2 energies show analogous trends. The ET in **TS5** (0.72e) is even higher than that in **TS3**. As a result, the geometries of the hydrocarbon moiety in **TS3** and **TS5** are strongly distorted. This compares favorably with the geometry of the isobutane radical cation complex with water (**6**); that is, the C−C bonds are shortened, and the four parallel C−H bonds are elongated. Note that this system also is allylic in nature and that the structures found for Cl_3^+ are quite comparable to those found for the allyl cation (Scheme 1). Fortunately, we were able to find transition structures for both pathways for Cl_3^+; however, due to the lack of formation of stable initial complexes, the energies of these transition structures are not very meaningful quantitatively (note the negative energies as a consequence of these extremely exothermic reactions). We conclude that both pathways are very similar in energy.

The overall driving forces for the ET reactions of isobutane with the allyl cation, HCl_2^+, and Cl_3^+ can be estimated through eqs 1−3 (B3LYP(MP2)/6-31G**, kcal mol^{-1}), where the electrophiles act as outer-sphere ET oxidants for isobutane, resulting in the formation of the *free* isobutane radical cation.[80] Even for such extreme cases, the oxidations of isobutane with chlorine electrophiles are exergonic (eqs 1 and 2). In contrast, the ET to the nonoxidizing allyl cation (eq 3) is strongly endergonic.

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(79) The third type of reaction is a proton transfer from HCl_2^+ to the alkane; however, in the CH_4 + HCl_2^+ reaction, chlorination products are mainly formed (ref 78).
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$$(CH_3)_3CH + HCl_2^+ = (CH_3)_3CH^{\bullet+} + HCl_2^{\bullet} \qquad \Delta_rG_{298} = -14.8\ (-5.4) \quad (1)$$

$$(CH_3)_3CH + Cl_3^+ = (CH_3)_3CH^{\bullet+} + Cl_3^{\bullet} \qquad \Delta_rG_{298} = -12.2\ (-4.8) \quad (2)$$

$$(CH_3)_3CH + [H_2CCHCH_2]^+ = (CH_3)_3CH^{\bullet+} + [H_2CCHCH_2]^{\bullet} \qquad \Delta_rG_{298} = +45.4\ (+64.5) \quad (3)$$

We now address the relevance of the H-coupled ET activations for other alkanes. Experimental data are available for the reactions of HCl_2^+ and Cl_3^+ with methane;[39,78] these lead to mixtures of $[H_3C-Cl-H]^+$ and $[H_3C-Cl-Cl]^+$. The kinetically controlled formation of $[H_3C-Cl-Cl]^+$ cannot be explained in terms of an electrophilic C−H insertion of Cl_3^+. Guided by the above findings, we have found transition structure **TS6** (Figure 2) displaying an elongated C−H bond (1.172 Å), describing the linear H-abstraction by Cl_3^+ from methane analogous to **TS5** located for isobutane. The resulting methyl cation complex can recombine with HCl or Cl_2 to form $[H_3C-Cl-H]^+$ or $[H_3C-Cl-Cl]^+$, respectively. Because of the higher I_p of CH_4,[81] the electron transfer from methane to Cl_3^+ in **TS6** is significantly smaller (ca 0.3e) than that for isobutane (**TS5**). As a consequence, the barrier for the H-coupled CH_4 ET-oxidation with Cl_3^+ is higher ($\Delta G^{\ddagger}_{298} = 22.9$ kcal/mol at B3LYP).

Isobutane Activation with Polyhalogen Species. To model the experimentally known functionalizations of alkanes in halogen solutions (typically neat Br_2), and to address the question of solvation as well as molecularity, we also computed (B3LYP/6-31G**) the reactions of isobutane with moderately electrophilic Hal_5^+ and Hal_7^+ species. We varied the type of Hal^1 that directly participates in the C−H attack (Figure 3) using a number of Cl atoms as a model for the secondary electrophilic shell. While the C−H activations with $Hal^1Hal_2^+$ are almost barrierless for isobutane (**TS5** and **TS7**, the $\Delta G^{\ddagger}_{298}$ values are similar to the above B3LYP/6-311+G**//B3LYP/6-31G** results), the more stabilized $Hal^1Hal_4^+$ and $Hal^1Hal_6^+$ cations (**TS8** and **TS9**, respectively, Figure 3) show substantial barriers. These depend mostly on the nature of the Hal^1 atom that directly abstracts the hydrogen from the C−H bond. Accumulation of halogens increases the barriers considerably from Hal_3^+ to Hal_5^+. The barriers for Hal_7^+ are only slightly higher than those for Hal_5^+; the highest barriers were generally observed for $Hal^1 = Br$. **TS8** and **TS9** are similar to the electron-transfer **TS7**, but the charge transfer from isobutane to the electrophilic oxidant varies (from 0.12e for **TS8**, $Hal^1 = Hal^2 = I$ to 0.56e for **TS9**, $Hal^1 = Cl$).

Similar trends were found for protonated polyhalogen reagents: the reaction of HCl_2^+ with isobutane is either barrierless (**TS3**, $Hal = Hal^1 = Cl$) or accompanied by a low barrier (5.6 kcal/mol for the reaction with HBr_2^+, **TS10**). For the protonated reagents $Hal^1Hal_3H^+$ (**TS11**), the barriers are virtually identical to those for $Hal^1Hal_4^+$ (**TS8**). Note that protonation of the abstracting halogen ($Hal^1HHal_3^+$, **TS12**) slightly lowers the barriers (10.8 and 18.9 kcal/mol for **TS12**, $Hal^1 = Cl$ and Br, respectively).

Adamantane Activation with Polyhalogen Species. Among the most intriguing C−H halogenation reactions is the practically useful bromination of adamantane (Scheme 4) that occurs in liquid Br_2 regiospecifically (100% of 1-bromoadamantane forms).[41,51] Similarly, only 1-adamantyl derivatives form in the related reactions of adamantane with I^+Cl^-[21] and I^+Br^-[61] in CCl_4. The heterolytic mechanism of these reactions was confirmed by a number of authors (catalysis by Lewis acids, tolerance toward light and radical starters,[82] the incorporation of the *nucleophilic* part of the reagent in halogenations with mixed halogens).[41] The regioselectivities of the halogenation of adamantane with free radicals are distinctly different (3°:2° = 4−6 for bromination[83] and 2−3 for chlorinations,[84] Scheme 4).

We extended our computations to the reactions of adamantane with some polyhalogen cations Hal_n^+ to model systems for which experimental data in the condensed state are available. We computed the activation step for the adamantane halogenations with Hal_n^+ ($n > 1$) and found transition structures **TS13** and **TS14** which are similar to those for the activation of the 3° C−H bond of isobutane (**TS8** and **TS9**).

There is a combination of several experimental peculiarities in the polar halogenations of adamantane that has been left unexplained (i−iv, see Introduction). Returning to the questions and observations posed initially, a straightforward explanation for (i) is that positively charged polarized halogen Hal_n^+ species form more easily in the presence of Lewis acids.[51] The observed high reaction orders (ii) for noncatalytic reactions can be explained with our model, as Hal_5^+ and Hal_7^+ as well as the Hal_4H^+ species are able to activate C−H bonds efficiently (further solvation of the electrophile with more halogens (Hal_9^+) changes the barriers only slightly).

Among the protonated polyhalogen species, the lowest barriers were computed for Hal_4H^+ cations (vide supra), which can form in the course of the halogenation as HHal is produced in the H-abstraction from the hydrocarbon. Because protonation of the halogen affects the barriers for the H-coupled ET process for isobutane (**TS12**), we also compared the experimental kinetics of the adamantane bromination in pure Br_2 versus Br_2 saturated with HBr and found that the reaction is faster in the presence of HBr. The pseudo-first-order rate constant for the bromination in pure bromine is $k^{obs} = 0.53 \pm 0.03 \times 10^{-4}\ s^{-1}$, while it is $0.79 \pm 0.04 \times 10^{-4}\ s^{-1}$ in Br_2 saturated with HBr. The question is what kind of polyhalogen electrophiles form in the Br_2/HBr system, enabling heterolytic halogenation to compete or even to suppress the more typical homolytic path. As shown in Figure 5, formation of the Br_nH^+ species via the $HBr + (n + m)Br_2 = [(Br_2)_nH]^+ + [Br(Br_2)_m]^-$ reaction becomes more favorable than homolytic $Br_2 \rightarrow 2Br^{\bullet}$ dissociation ($\Delta H_{298} = +49.0$ kcal/mol, B3LYP/6-31G**) only for $(n + m) = 8$.

Thus, polar and homolytic reactions may compete only at high bromine concentrations in agreement with experimental observations.[41] The computed "$n + m$" value (Figure 5) reproduces the experimental bromination reaction order (ca. 7.5, Figure 6) in Br_2 exceptionally well and validates our computational model. The experimental activation energy for ada-

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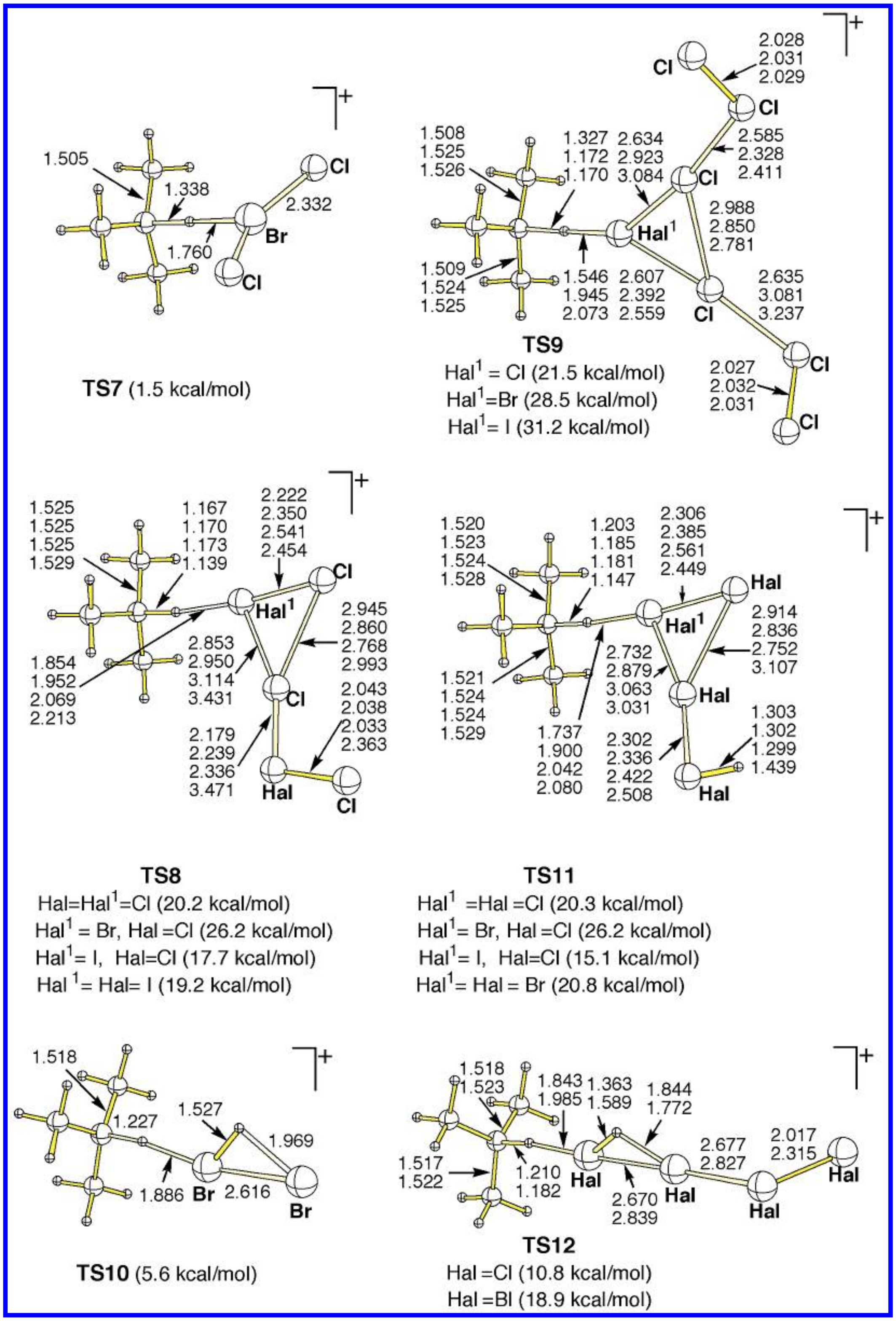
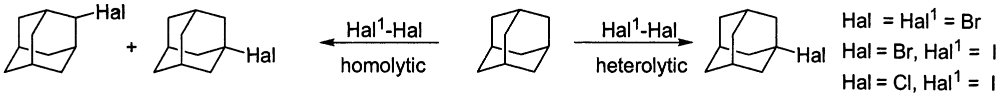


Figure 3. The transition structures and the barriers for H-coupled electron transfer from isobutane to some polyhalogen cations {relative $\Delta G^{\ddagger}_{298}$ in kcal/mol at B3LYP/6-31G**(H, C, Cl, Br) and 3-21G* (I)}.

Scheme 4



mantane bromination ($\Delta G^{\ddagger}_{298} = 18.6$ kcal/mol) also is in good agreement with the computed barrier via **TS14**, Hal^1 = Br (21.9 kcal/mol).

Yet, the amazing 100% regiospecificity for the halogenation (iii) has not been explained. Involvement of adamantyl cations cannot be the reason because the difference in the stability of

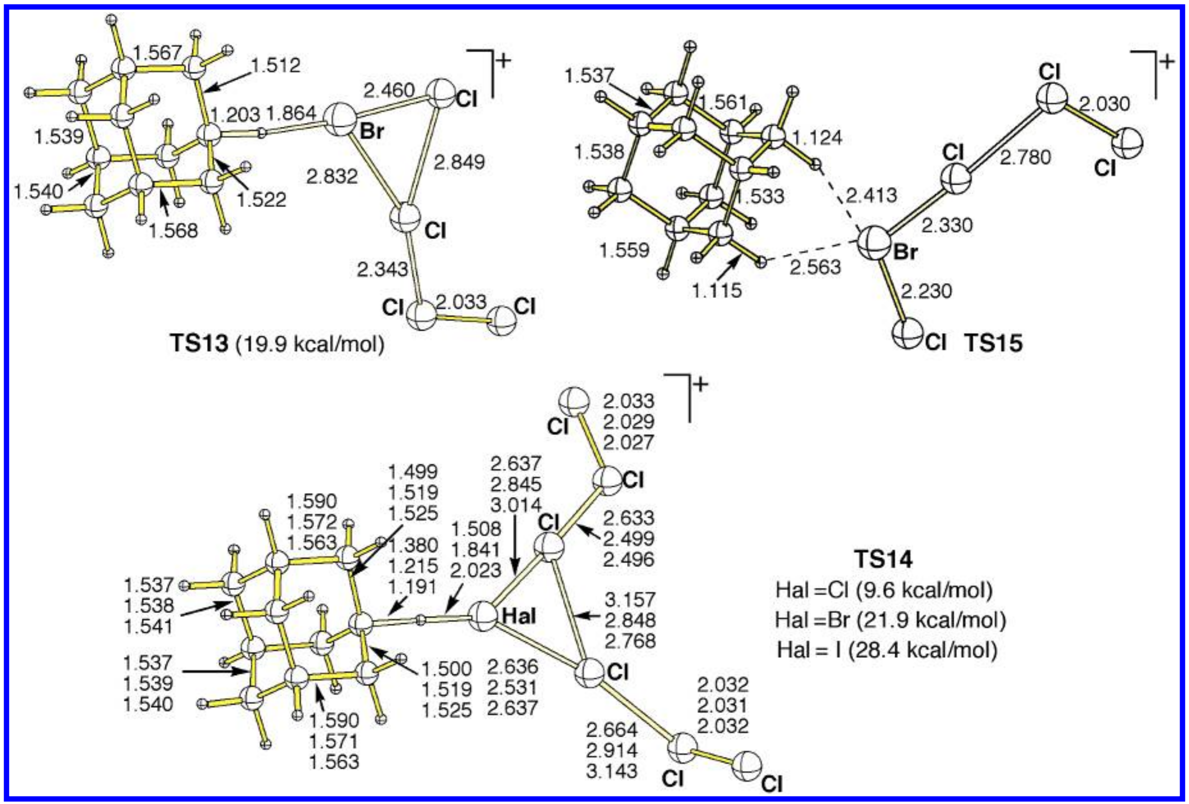


Figure 4. The barriers for the reactions of polyhalogen cations involving the 3° C−H (**TS13** and **TS14**) and 2° C−H (**TS15**) bonds of adamantane $\{\Delta G^{\ddagger}_{298}$ in kcal/mol at B3LYP/6-31G**(H, C, Cl, Br) and 3-21G* (I)$\}$.

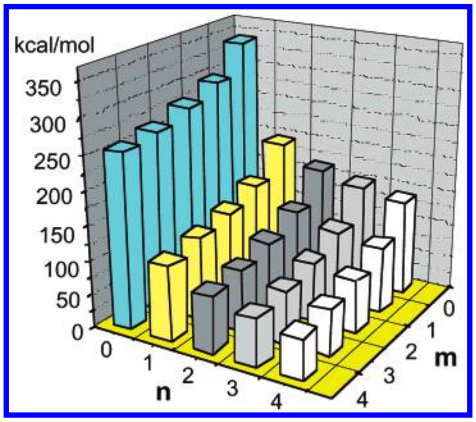


Figure 5. The heterolytic dissociation of Br_2 in the presence of HBr forming the $[(Br_2)_nH]^+$ electrophilic species via the $(n + m)Br_2 + HBr = [(Br_2)_nH]^+ + [Br(Br_2)_m]^-$ reaction (Δ_rH_{298} in kcal/mol at B3LYP/6-31G**). The reaction approaches the endothermicity of homolytic reaction $Br_2 \rightarrow 2\ Br^{\bullet}$ (+49.0 kcal/mol) only at $n + m = 8$.

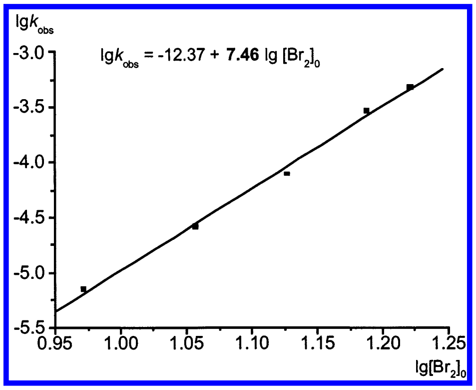


Figure 6. The experimental dependence of the observed rate constant k_{obs} for adamantane bromination on the initial molar concentration of Br_2 in CCl_4.

1- and 2-adamantyl cations (12 kcal/mol) may explain only the selectivity of thermodynamically controlled substitution, which is not the case for bromination.[85,86] The 1- and 2-adamantyl radicals have almost the same heats of formation;[87] that is, the 2° and 3° C−H bonds of adamantane have approximately the same strength. The H-coupled ET mechanism offers an excellent explanation for the observed regiospecificities. Significant charge transfer from the adamantane cage to the Hal_n^+ cations (in **TS14** this ranges from 0.33e for Hal^1 = I to 0.74e for Hal^1 = Cl) leads to hydrocarbon moieties resembling the adamantane radical cation. As this radical cation has only one C_{3v}-minimum with elongated C−C and C−H bonds,[40] only 3° C−H-coupled electron transfer agrees with concomitant polarization of the adamantane cage. The ET through a 2° C−H bond is highly unfavorable, and **TS15** for the activation of the secondary position describes the migration of the electrophile from one bonding position in the complex to another rather than the H-abstraction process. Only **TS15** (Hal^1 = Br) is shown (Figure 4), but our findings also apply to other Hal_n^+ species interacting with the 2° C−H bonds of adamantane. The structures of the adamantane moieties in **TS13** and **TS14** (Figure 4) are geometrically similar to that of the complex of the adamantane radical cation with water.[41] Analogous to polar halogenations, high 3° C−H substitution selectivities were previously observed

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Table 1. Computed H/D KIEs (298.15 K, 1.0 atm) for the Halogenation of Adamantane with Cl_7^+, $BrCl_6^+$, and ICl_6^+

structure	A_H/A_D	$\Delta\Delta$ZPVE‡ (H/D)	KIE (Arrhenius)	KIE (Bigeleisen)	KIE (RRKM)
TS14[a] Hal^1=Cl	1.18	1.12	7.8	6.4	4.5
TS14[a] Hal^1=Br	1.66	0.69	5.3	3.3	4.4
TS14[a] Hal^1=I	1.24	0.51	3.0	2.4	4.5

[a] Computed for the C−D bond of AdD_4 versus the C−H bond of AdH_4.

for oxidation of adamantane with photoexcited 1,2,3,4-tetracyanobenzene through an outer-sphere ET process involving the adamantane radical cation,[88] or with highly electrophilic radicals such as $NO_3^\bullet$.[89,90]

Comparisons of experimental and computed KIEs are among the most powerful tools in mechanistic studies.[91−93] The available k_H/k_D KIE value for the adamantane bromination is hard to verify by proper computations because of the system size (the Br_n^+-containing species must be computed at a high level of theory). Hence, we also measured the KIEs for the chlorination of adamantane with I^+Cl^- in CCl_4 for a mixture of AdH_4 and 1,3,5,7-tetradeuterioadamantane (AdD_4) using the GC/MS experimental technique we described previously for adamantane halogenations under phase-transfer conditions.[94,95] The measured KIEs ($k_H/k_D = 3.1 \pm 0.3$ in CCl_4) are slightly lower than those for the bromination ($k_H/k_D = 3.9 \pm 0.2$[41]). We computed the KIEs via **TS14** using different approaches (Arrhenius treatment with computed A_H/A_D and $\Delta E_a^H - \Delta E_a^D$,[92] with the Bigeleisen equation,[96] and utilizing RRKM theory,[97] Table 1). The high KIEs reflect the linear geometries of the C···H···Hal fragment of the TSs. Thus, the high experimental KIEs (iv) can be rationalized with the computed geometries of the TSs for the H-coupled electron transfer. These KIE values also compare well with H-radical abstractions from adamantane by trihalomethyl radicals (KIE here = 4−5).[94] Again, we emphasize the close relationship of these formally electrophilic reactions with radical reactions by means of involvement of intermediate radical cations or radical cation-like transition structures.

The combined experimental and computational data provide a mechanistic understanding of alkane C−H activations with oxidizing electrophiles and, together with our previous studies on C−C activations,[17,40,41,98,99] demonstrate the importance of electron transfer in alkane halogenation reactions. Relatively weak delocalized electrophilic species such as Hal_n^+ ($n > 5$) may be effective H-abstractors similar to halogen radicals. The key difference in the radical H-abstraction process is that the activation with the electrophile is accompanied by an ET through the linearly H-coupled $[R\cdots H\cdots E]^+$ fragment. The selectivities of these transformations may be understood in terms of involving hydrocarbon radical cations as TS moieties and intermediates.

Concluding Remarks

We identified two distinctly different alkane C−H activation modes with electrophiles: strongly bonding (electrophilic) and weakly bonding (oxidative). For nonoxidizing electrophiles (like carbocations), triangular three center-two electron interactions are favorable, in agreement with Olah's suggestions. The C−H activations with weakly electrophilic oxidants such as Hal_n^+ or $Hal_{n-1}H^+$, however, are best visualized as concerted H-coupled electron-transfer reactions. The regioselectivities can only be rationalized in terms of hydrocarbon moieties being largely radical cationic in character in the corresponding transition structures. This inner electron-transfer mechanism is operative for strong oxidizers and possesses, on the basis of the nature of the TS and the H/D kinetic isotope effects, some common features with C−H abstractions with halogen radicals, involving *linear* $[R\cdots H\cdots E]^+$ fragments.

In a broader context, our findings allow one to distinguish between oxidative versus electrophilic pathways. In the purely electrophilic picture, which is based on alkane σ-bond basicity,[4,5,7,8,10,100] the electrophile is viewed as inserting into alkane C−H (or C−C) bonds directly. The intermediate, functionalized cations then rearrange and give, in virtually all cases, the thermodynamically most favorable product. As a matter of fact, this is the very reason for the importance of classical electrophilic alkane activation because it provides convenient access to higher-grade (more branched) alkane fuels. However, while these *functionalizations* are selective (providing mostly one thermodynamic product), the *activations* are not. In marked contrast, oxidative (i.e., by means of inner or outer electron transfer) activation can be selective if a particular radical cation (or radical cation moiety of a transition structure) ensues. That is, the structure of the radical cationic hydrocarbon fragment is ultimately responsible for the selectivity.

As the selectivities of radical reactions often are traced back to polar effects, one may argue that the same is true for electrophilic alkane activation, which, as evident from the present work, also displays features of radical reactions. In other words, alkane activations with radicals and with electrophiles (which may incidentally also be radicals) display similar features at different ends of the same mechanistic spectrum.[2] In contrast to radical reactions, the importance of polar effects is maximized in the case of electrophile-oxidizers which, in turn, display the highest selectivities.

The presented concepts are also applicable to other electrophile-oxidizers or alkanes. Such studies are well underway in our laboratories and will be reported in due course.

Computational Methods

Geometries were optimized at the MP2/6-31G**[101] and B3LYP/6-31G**[102] levels of theory including frequency analyses to disclose the nature of the stationary points (Nimag = 0 for minima and Nimag

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= 1 for transition structures) as implemented in the Gaussian 98 program package.[103] Relative energies are ΔG_{298}-corrected at the B3LYP/6-311+G**//B3LYP/6-31G** and MP2/6-311+G**//MP2/6-31G** levels. The ΔG_{298} values for the polyhalogen species were computed only at the B3LYP/6-31G** (H, C, Cl, Br); 3-21G* (I) level due to the considerable size of the systems. The reaction pathways along both directions from the transition structures were followed by the IRC method.[104]

Experimental Section

Kinetics of Liquid-Phase Bromination of Adamantane. The kinetics of adamantane bromination were studied in Br_2/CCl_4 mixtures (concentrations of Br_2 varied from 9 to 15 M). Neat bromine was kept over KBr, dried over P_2O_5, and distilled from and stored over P_2O_5. Kinetic experiments were run with freshly distilled bromine. Adamantane was recrystallized from heptane and freshly sublimed. CCl_4 was distilled over P_2O_5. A sample of adamantane was dissolved in CCl_4, the solution was mixed with bromine, and P_2O_5 was added (in an amount equal to that of adamantane). The probes were poured onto an excess of a saturated solution of Na_2SO_3, extracted with hexane, and dried over Na_2SO_4. The concentrations of the reactants and products were followed by GC. The logarithms of the rate constants for the adamantane bromination show a linear dependence on the logarithms of the initial bromine concentrations. The pseudo-first-order rate constants were used for the KIE measurements. In a typical kinetic experiment both for adamantane and for 1,3,5,7-tetradeuterioadamantane $[AdH(D)]_0 = 0.2$ mol L^{-1}, $[Br_2]_0 = 13.4$ mol L^{-1}, and $[CCl_4]_0 = 5.6$ mol L^{-1}, the pseudo-first-order bromination rate constants were at 25 °C and $[Br_2]_0 = 16.62$ mol L^{-1}, $k = 4.81 \times 10^{-4}$ s^{-1}; 15.40 mol/L, $k = 2.91 \times 10^{-4}$ s^{-1}; 13.40 mol L^{-1}, $k = 0.78 \times 10^{-4}$ s^{-1}; 1.39 mol L^{-1}, $k = 0.26 \times 10^{-4}$ s^{-1}; 9.38 mol L^{-1}, $k = 0.0715 \times 10^{-4}$ s^{-1}. These data were used for the determination of the reaction order in bromine as the gradient of the slope of log k versus log$[Br_2]$. The calculated reaction order in bromine was 7.46. At $[Br_2]_0 = 13.4$ mol L^{-1}, $[AdH]_0 = 0.2$ mol L^{-1}, $k^{293} = 0.62 \times 10^{-4}$ s^{-1}; $k^{298} = 0.78 \times 10^{-4}$ s^{-1}; $k^{303} = 0.90 \times 10^{-4}$ s^{-1}; $k^{308} = 1.16 \times 10^{-4}$ s^{-1}; $k^{313} = 1.43 \times 10^{-4}$ s^{-1}, giving $\Delta H^{\ddagger} = 6.85$ kcal mol^{-1} and $\Delta S^{\ddagger} = -52.8$ cal mol^{-1} K^{-1}.

Kinetics of Competitive Chlorination of Adamantane and 1,3,5,7-Tetradeuterioadamantane with ICl. Two milliliters of the solution of 68.0 mg of adamantane, 70.0 mg of 1,3,5,7-tetradeuterioadamantane, and 258.8 mg of ICl was kept at 23 °C in CCl_4. The probes were taken with a syringe and poured in a mixture of saturated solution of Na_2SO_3 and ether. The organic layer was analyzed by GC/MS. Relative concentrations of adamantane, 1,3,5,7-tetradeuterioadamantane, 1-chloroadamantane, and 1-chloro-3,5,7-trideuterioadamantane were obtained from mass selective chromatograms. Calculated pseudo-first-order rate constants were $k_H^{298} = (1.29 \pm 0.02) \times 10^{-4}$ s^{-1}, $k_D^{298} = (0.41 \pm 0.01) \times 10^{-4}$ s^{-1}, and $k_H/k_D = 3.1 \pm 0.3$ from the results of three kinetic experiments.

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Supporting Information Available: *Xyz*-coordinates and absolute energies for all computed species (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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