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Oxidative Single-Electron Transfer Activation of σ-Bonds in Aliphatic Halogenation Reactions

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Abstract: The reactions of a series of structurally related large-ring propellanes with iodine monochloride were studied experimentally and computationally. In the case of 1,3-dehydroadamantane (**1**) and [3.3.1]propellane (**2**) free-radical addition was observed. [3.3.2]Propellane (**3**) and 3,6-dehydrohomoadamantane (**4**), which are less prone to radical attack, selectively form products of formal double nucleophilic (oxidative) addition, e.g., dichloro (in ICl/CH_2Cl_2), dimethoxy (in ICl/CH_3OH), and diacetamino (in ICl/CH_3CN) derivatives under otherwise identical conditions. Single-electron transfer pathways involving the alkane radical cations are proposed for the activation step for aliphatic hydrocarbons with relatively low oxidation potentials such as cage alkanes. Similar mechanisms are postulated for the activation of the tertiary C−H bonds of adamantane based on H/D-kinetic isotope effect data. The latter compare well to the k_H/k_D value for hydrogen atom loss from the adamantane radical cation (measured 2.78 ± 0.21 and computed 2.0) and differ considerably from the kinetic isotope effects for electrophilic C−H bond activations (i.e., hydride abstraction) or for loss of a proton from a hydrocarbon radical cation ($k_H/k_D = 1.0-1.4$; computed 1.4). Hence, the reactions of alkanes with elementary halogens and other weak electrophiles (but strong oxidizers) do not necessarily involve three-center two-electron species but rather occur via successive single-electron oxidation steps. Upon C−C or C−H fragmentation, the incipient alkane radical cations are trapped by nucleophiles.

Introduction

The selective activation and functionalization of alkanes, despite extensive efforts, still is highly challenging and is considered a "holy grail" in chemistry.[1−6] Different methods for alkane activation evolved, e.g., free radical reactions, enzymatic transformations, as well as carbene or organometallic insertions.[5,7,8] Perhaps the most intriguing mechanistic proposals are related to electrophilic alkane conversions believed to occur via formation of three-center two-electron (3c-2e) transition structures or intermediates (Scheme 1).[9−13] Despite the fact that many electrophilic reagents widely used in alkane activations are known to have both electrophilic and oxidizing properties, single electron transfer (SET) oxidations of hydrocarbons with concomitant formation of radical cations followed by proton (or hydrogen atom) loss[14−17] or fragmentation[18−22] have largely been left unexplored. In on our previous experimental and computational studies[23−25] we found that SET pathways are quite important if not decisive for alkanes with low ionization potentials such as large-ring propellanes (C−C bond oxidation) or adamantanes (C−H bond oxidation) in their reactions with

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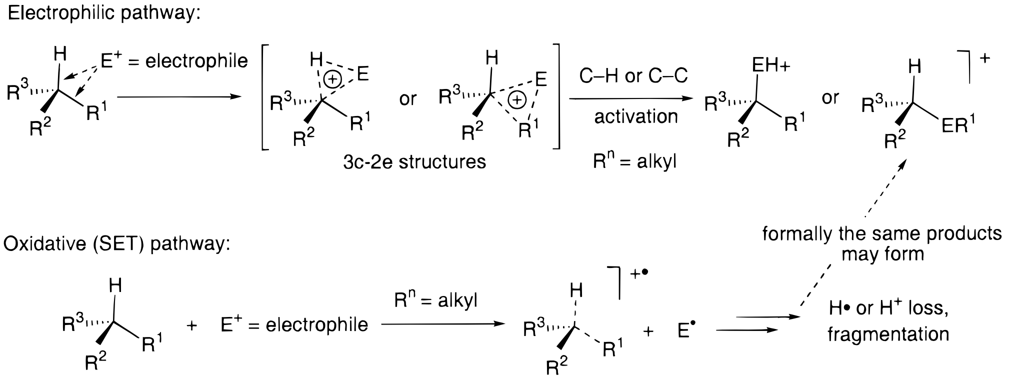
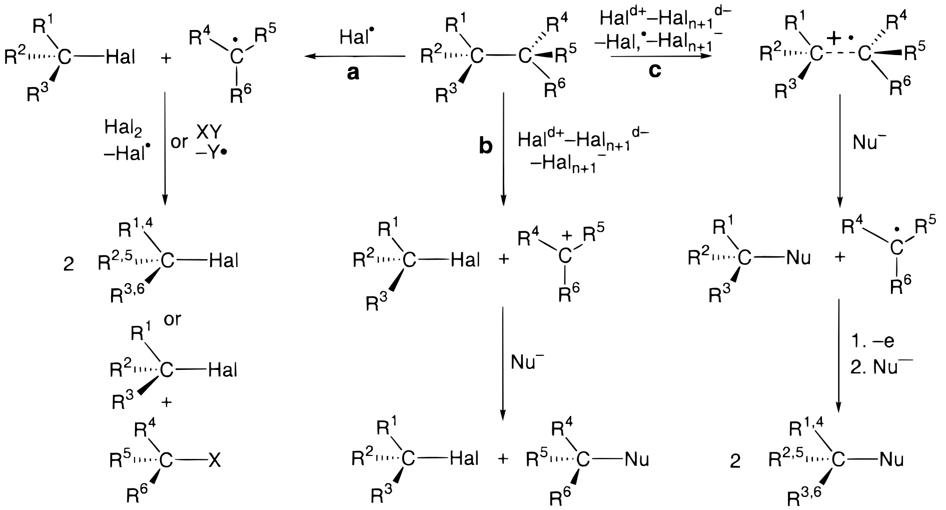
Scheme 1. Electrophilic (formation of 3c-2e species) and Single-Electron Oxidation Pathways (i.e., through alkane radical cations) for Aliphatic Hydrocarbon Functionalization[a]



[a] These two pathways represent the two borderline cases of the reactivity spectrum whereby the first may be considered as an inner-sphere and the second as an extreme case for an outer-sphere ET process.[40]

Scheme 2. Generalized Mechanistic Picture for Alkane C–C Bond Halogenations



nitrosonium (NO^+) and nitronium (NO_2^+) electrophiles (e.g., in the form of their salts, $NO^+BF_4^-$ and $NO_2^+BF_4^-$).

Mechanistic interpretations of polar C–H halogenation reactions are often clouded by the inability to identify the nature of the proposed transients (which may even be transition structures) and the departing groups or atoms (e.g., H^-, $H^\bullet$, or H^+). As cage hydrocarbon halogenations are an intriguing example, we will first focus our attention on the mechanisms of σ_{C-C}-bond halogenations which have been studied involving strained propellanes[26–28] and bicyclobutanes.[29,30] Possible mechanistic scenarios for the addition of elementary halogens to saturated σ_{C-C} bonds are depicted in Scheme 2. Radical chain halogenations (pathway **a**) normally occur in nonpolar solvents upon photochemical or thermal initiation.[31–33] Polyhalomethanes react quickly with some small-ring propellanes also via free-radical pathway **a**.[34] Radical mechanisms also were proposed for some other halogenating reagents such as $PyH^+Br_3^-$.[35,36]

Evidence for pathway **b** (electrophilic) comes from nucleophilic trapping of cationic intermediates in polar solvents. For instance, the iodination or bromination of [1.1.1]propellane in methanol involves the formation of the 3-halobicyclo[1.1.1]pent-1-yl cation.[37] Electrophilic chlorination and bromination of cyclopropane also appears to proceed via haloethyl ions.[38,39]

Elementary halogens also are oxidizing agents; the mechanisms involving initial SET followed by formation of hydrocarbon radical cations are depicted in pathway **c**. This mechanism was proposed for the reaction of bicyclo[1.1.0]butane-1-carbonitrile with bromine in methanol,[41] but was later criticized based on partial analysis of the thermodynamics of this system.[30] The SET oxidation of strained alkanes with bromine was claimed to be endergonic and slow.[30]

These mechanisms may be examined in more detail using mixed halogens such as iodine monochloride (I^+Cl^-). This reagent has successfully been used for mechanistic studies of adamantane C–H halogenations[42] and aromatic substitution

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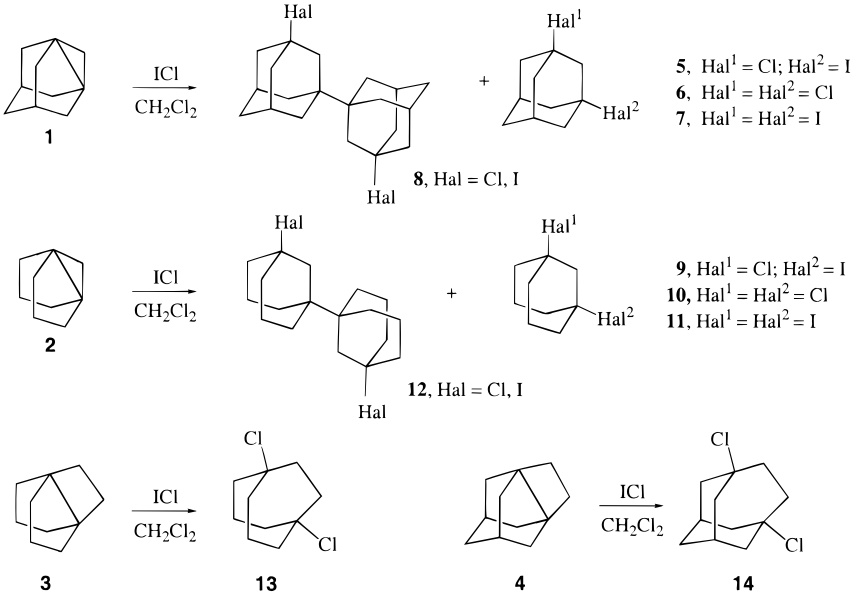
Scheme 3. Addition of ICl to Propellanes **1−4**



reactions.[43,44] In the latter case, it was shown that some aromatic compounds with low ionization potentials undergo chlorination rather than iodination, and this fact could only be attributed to an SET oxidation of the hydrocarbon. Surprisingly, there is only one study on the reactions of propellanes with mixed halogens, namely the addition of I^+Cl^- to [1.1.1]propellane which resulted in the formation of complex mixtures of halogenated compounds.[37]

It was in this context that we began to examine the reactivity of some large-ring propellanes (**1−4**) which are more stable than [1.1.1]propellane avoiding side reactions such as fragmentation and isomerization. These propellanes are pertinent hydrocarbon models for studying the mechanisms of σ_{C-C}-bond halogenations because the C−C bond reactivities can be varied considerably by changing the ring size. Among other questions addressed in the present paper, we will reveal details of C−H halogenation mechanisms of adamantane[45] and other cage hydrocarbons.

Results and Discussion

C−C Bond Halogenations. The reactivity of C−C bonds varies widely in hydrocarbons **1−4** (Scheme 3). 1,3-Dehydroadamantane (**1**) with an inverted geometry[46] at the quaternary carbons is highly reactive and adds various reagents such as proton acids,[47] oxygen,[48] and bromine[48] at low temperatures. [3.3.1]Propellane (**2**) is less reactive than **1** toward oxygen or acetic acid, but could also be brominated with elementary bromine at low temperatures.[32,33] [3.3.2]Propellane (**3**) is known to be reactive toward trifluoroacetic acid only under prolonged heating.[49] In contrast, 3,6-dehydrohomoadamantane (**4**) does not react with oxygen, peroxides, or proton acids, but, as adamantane, slowly reacts with liquid bromine upon heating.[50] Thus, propellanes **1−4** cover a wide range of σ_{C-C}-bond reactivities with only minor changes in structure.[25]

Cyclopropane-containing propellanes **1** and **2** react with ICl in CCl_4, CH_2Cl_2, and THF with formation of complex mixtures of halogenated products **5−12** (Scheme 3). These mixtures of products as well as the formation of dimers **8** and **12** are clear indications for a free-radical halogenation mechanism. This is consistent with earlier observations that the bromination of **2** in the dark occurs via a free-radical pathway.[32,33]

In contrast, the addition reactions of ICl to **3** and **4** under similar reaction conditions are highly selective as only dichloro products **13** and **14** were found. This selectivity is not expected for a radical mechanism (pathway **a**, Scheme 2). Formal addition of two nucleophiles (Cl^-) to the central C−C bonds provides strong support for oxidative activation pathway **c** for **3** and **4**. As an example, Scheme 4 outlines SET from **4** to I^+Cl^- leading to a radical ion pair of $\mathbf{4}^{+\bullet}$ and $I^\bullet Cl^-$. Nucleophilic trapping of $\mathbf{4}^{+\bullet}$ produces radical **A** which may undergo further oxidation to cation **B**, followed by a second nucleophilic addition.[51,52] This scheme is in accord with the observed 2:1 ICl to hydrocarbon stoichiometry. Intermediate formation of radical **A** in the course of the oxidative addition was confirmed by using $BrCCl_3$ as a radical trapping reagent: The halogenation of **4** by ICl in $BrCCl_3$ was accompanied by formation of 15% of 3-bromo-6-chlorohomoadamantane.

The reaction of **4** with ICl in nucleophilic solvents also proceeds as a formal double nucleophilic addition with formation of 3,6-dimethoxyhomoadamantane (**15**) in ICl/CH_3OH and 3,6-diacetaminohomoadamantane (**16**) in ICl/CH_3CN. Hence, cationic intermediates are trapped by nucleophilic solvents (Scheme 4) as previously observed for the oxidation of **4** with nitronium[53] and nitrosonium[24] reagents, under anodic oxidation,[54] and photooxidation.[24] It is important to note that

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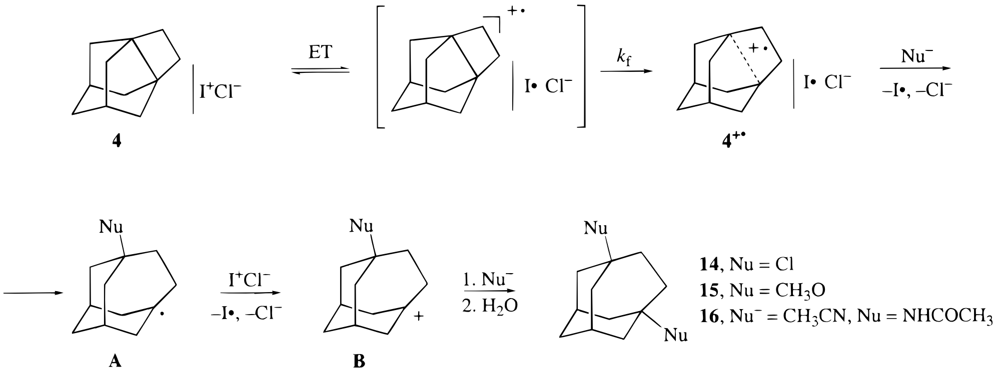
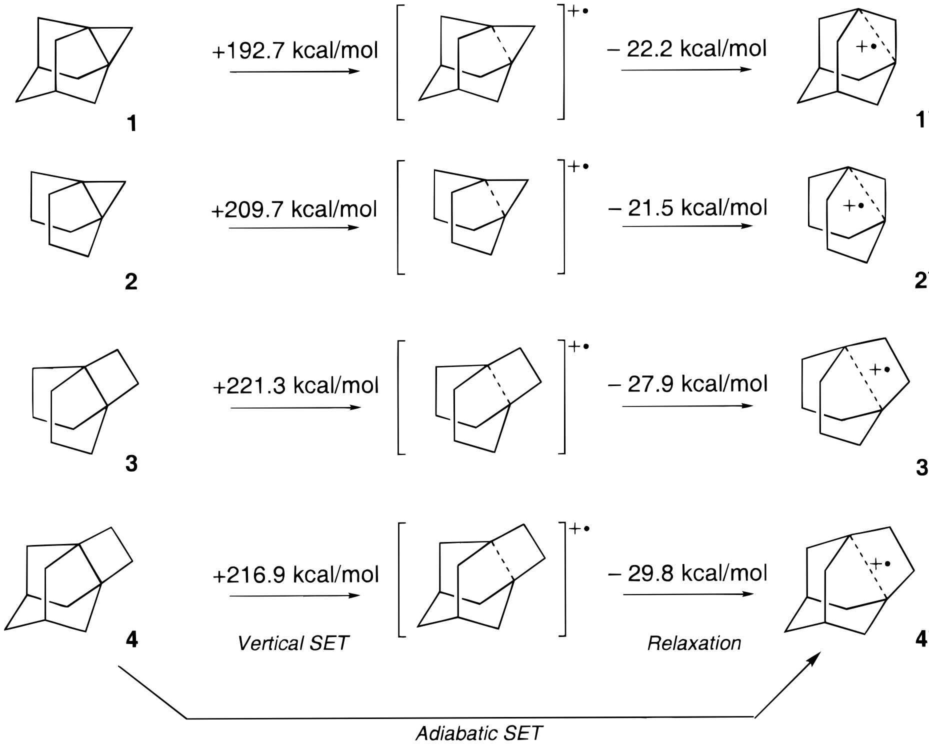
Scheme 4. SET Mechanism for the Halogenation of **4** with ICl[a]



[a] k_f designates the rate constant for C−C bond fragmentation.

Scheme 5. Relative Reaction Energies for Vertical SET Oxidation and σ_{C-C} Bond Fragmentation for Propellanes **1**−**4** at MP2/6-311+G**//MP2/6-31G*



SET from **1**−**4** to ICl is energetically favorable due to the relatively low ionization potentials of these alkanes.[25] The vertical ionization potentials[55] of **1** (8.35 eV), **2** (9.09 eV), **3** (9.59 eV), and **4** (9.41 eV)[25] are much lower than the electron affinity of I^+ (10.4 eV).[56] This value presents an upper limit but is probably a good approximation for the electron affinities of $(ICl)_n$ clusters.[5,7,8] The simplest model reaction ($IClH^+ + e^- \rightarrow I^\bullet + HCl$) to estimate the oxidative properties of ICl is 257.1 kcal mol^{-1} (11.1 eV) exothermic (at B3LYP with a MIDI![57] basis set for iodine and 6-31G* for hydrogen and chlorine).

The differences between the reactivities of cyclopropane-containing propellanes **1** and **2** and their cyclobutane analogues **3** and **4** can be rationalized in terms of the pronounced sluggishness of **3** and **4** toward radical reagents. The radical addition to **1** and **2** is faster than SET oxidation with ICl; the opposite is true for **3** and **4**. As the electron transfer from the hydrocarbon to the oxidizer is reversible (Scheme 4),[58] the efficiency of the oxidation depends on the relative rate of radical cation fragmentation (k_f) and competitive reverse SET. Ionization from the propellane HOMO, located on the central C−C bond of **3** and **4**,[25] leads to elongation of this “half-broken” bond (adiabatic process) and is accompanied by strain decrease in the partially distonic[59] radical cation, making fragmentation energetically favorable. Radical cations $\mathbf{3}^{+\bullet}$ and $\mathbf{4}^{+\bullet}$, in fact, are formed *irreversibly*[60−62] under *adiabatic* ionization of the strained hydrocarbon, and oxidation proceeds efficiently. As shown in Scheme 5, the oxidative fragmentation is more

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[55] Vertical IPs were computed for the neutral hydrocarbon geometries where one electron was removed (i.e., a Franck−Condon state). As a consequence, these structures are not stationary and only serve as models for fast and reversible electron transfer in aliphatic hydrocarbons. This is the reason these “structures” are put in brackets in Schemes 4 and 5.

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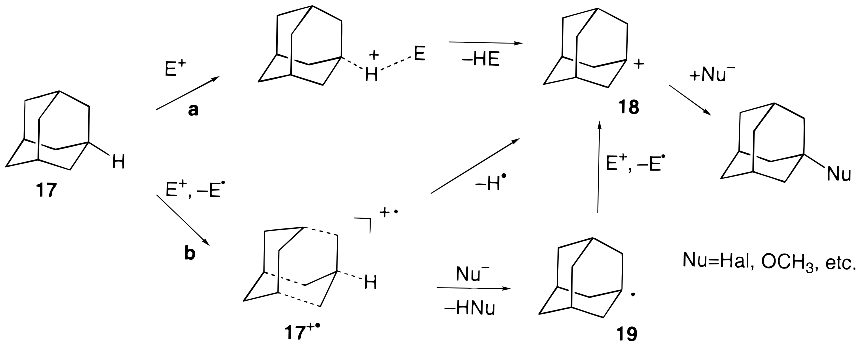
Scheme 6. Electrophilic and Oxidative Pathways for the Activation of a Tertiary C−H Bond of Adamantane



favorable for cyclobutane containing **3** and **4** due to larger central C−C bond elongation and more effective strain decrease in the resulting radical cations $\mathbf{3}^{+\bullet}$ and $\mathbf{4}^{+\bullet}$.

Hydrocarbon C−H Bond Halogenations. C−C bond breaking is only one of the many fragmentation pathways of hydrocarbon radical cations;[63] others include C−H bond cleavage as observed for adamantane (**17**) and some other hydrocarbons upon photooxidation[64−67] or anodic oxidation.[68−72] The two principal polar mechanisms for the reactions of aliphatic hydrocarbons with an electrophile (E^+), i.e., via “hydride abstraction” (**a**) and SET (**b**), are depicted in Scheme 6 for the adamantane case study. The SET pathway for the activation of **17** with NO_2^+ has been questioned by Olah,[73] and an electrophilic mechanism involving hydride abstraction as the rate-limiting step was proposed instead (path **a**). In previous mechanistic studies of adamantane C−H halogenations with Br_2[74] and ICl[42] electrophilic mechanisms also were proposed but never conclusively demonstrated. As adamantane has a relatively low ionization potential (experimental vertical IP 9.21−9.26 eV,[75,76] the computed adiabatic IP at MP2 is 9.5 eV),[24] SET oxidation must not be excluded a priori.

Many aliphatic substitution mechanisms are too difficult to be rationalized based on synthetic results only,[3] as both electrophilic and oxidative activation pathways are consistent with the available synthetic data. Therefore, we undertook studies utilizing H/D kinetic isotope effects (KIEs) to distinguish between electrophilic and oxidative pathways. KIEs are exceptionally valuable in mechanistic studies, in particular in combination with ab initio molecular orbital computations, which allow a more detailed rationalization of the measured KIEs.

Electrophilic Activation of the Tertiary C−H Bond of Adamantane. As shown previously by Schreiner et al.,[77,78] one possible pathway in the activation of methane and ethane with relatively stable electrophiles such as NO^+ involves direct carbon atom attack; similar findings were also reported by DePuy et al. for the reactions of BH_2^+ with these hydrocarbons.[79] In contrast, electrophilic attack of protonated hydrogen peroxide $H_3O_2^+$ (hydroperoxonium ion) on the tertiary C−H bond of isobutane is a hydride *abstraction* according to Bach and Su;[80,81] Scheme 7 summarizes these results, computed for adamantane.

Adamantane exothermically forms an initial complex (**20**, -10.3 kcal mol^{-1}) with the hydroperoxonium ion (Figure 1). Such alkane−electrophile complexes were suggested computationally[77,78] and verified experimentally.[82] The transition structure **21** for hydride abstraction from adamantane is characterized by an only slightly elongated C−H bond (1.14 Å vs 1.11 Å in **20**); the barrier for hydride abstraction with $H_3O_2^+$ is only 1.6 kcal mol^{-1}; the computed H/D KIE of this electrophilic reaction is very small ($k_H/k_D = 1.07$) and reflects the early character of the transition state.

Vanishingly low barriers for hydride transfer were also found for the reactions of alkanes with carbocations.[13] Computations at DFT and MP2 levels indicate that the “*formation of a stable tight intermediate complex and decomposition of the complex to the products*” occurs “*without activation energy*”.[83] As it appears rather difficult to determine meaningful activation barriers for these types of reactions, we used chemical ionization mass spectrometry (CI-MS) to estimate the KIE for electrophilic C−H bond activation by carbocations experimentally to distinguish between purely electrophilic and SET pathways. The relative rates for hydride abstraction from the adamantane bridgehead positions with the *tert*-butyl cation were determined from the CI-MS data for adamantane, alkyladamantanes, and their deuterated analogues using isobutane as the reagent gas (see Experimental Section for details). These experiments indicate that the KIEs for the electrophilic activation of the tertiary C−H bonds of adamantane indeed are quite low ($k_H/k_D = 1.05 \pm 0.10$) and in excellent agreement with our computed KIEs for the reaction of adamantane with $H_3O_2^+$.

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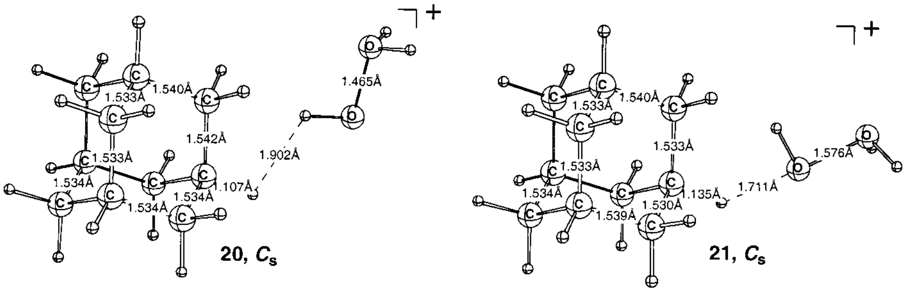
(79) DePuy, C. H.; Gareyev, R.; Hankin, J.; Davico, G. E.; Krempp, M.; Damrauer, R. *J. Am. Chem. Soc.* **1998**, *120*, 5086.

(80) We found an analogous transition structure for hydride abstraction from isobutane with the Cl_3^+ cation, modeling the electrophilic reaction with polarized dihalogen compounds. The geometry of the hydrocarbon moiety in this TS and the reaction barriers are quite similar to that found by Bach and Su for the hydroperoxonium ion reaction with isobutane.

(81) Bach, R. D.; Su, M.-D. *J. Am. Chem. Soc.* **1994**, *116*, 10103.

(82) Cacace, F.; de Petris, G.; Pepi, F. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 3507.

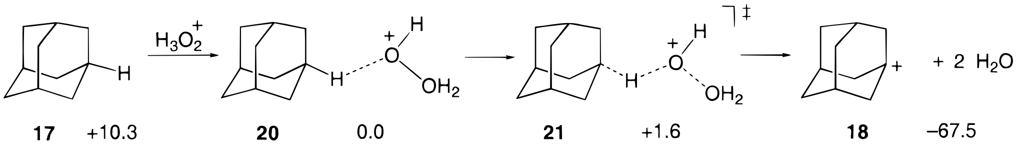
(83) Boronat, M.; Viruela, P.; Corma, A. *J. Phys. Chem. B* **1997**, *101*, 10069.



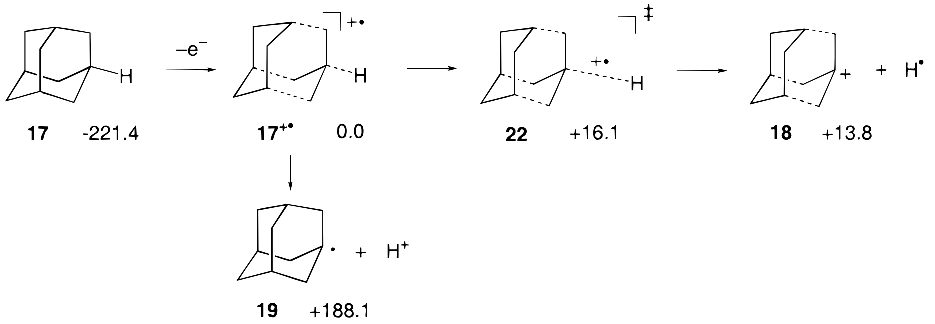
20, C_s **21, C_s**

Figure 1. MP2/6-31G* optimized geometries of the initial complex (**20**) and the transition structure for hydride abstraction (**21**) from adamantane with $H_3O_2^+$.

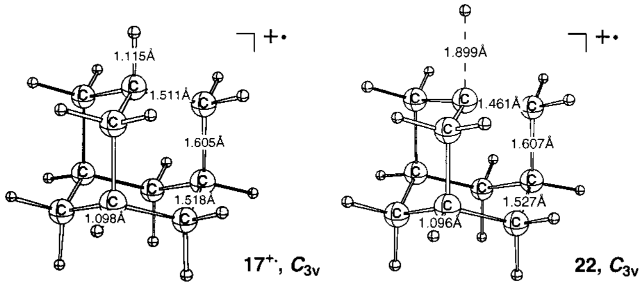
Scheme 7. Hydride Abstraction with the Hydroperoxonium Ion from a Tertiary C−H Bond of Adamantane {Relative Energies in kcal mol^{-1} at MP2/6-311+G**//MP2/6-31G* + ΔZPVE}



Scheme 8. Computed Hydrogen Loss from the Adamantane Radical Cation {Relative Energies in kcal mol^{-1} at MP2/6-311+G**//MP2/6-31G* + ΔZPVE}



This k_H/k_D value is quite different from the KIEs observed for typical adamantane C−H substitution reactions with stable electrophiles. The KIE for the bromination of adamantane in Br_2/CCl_4 for 1,3,5,7-tetradeuterioadamantane vs adamantane is 3.9 ± 0.2. This value is similar to the one found previously for adamantane nitroxylation ($k_H/k_D = 4.5 \pm 0.3$) with 100% nitric acid.[84] The KIEs for the reactions with *charged* nitrogen-containing electrophiles (NO_2^+ and NO^+ salts in CH_3CN) are 1.9−2.3.[85]



$17^{+\cdot}$, C_{3v} **22, C_{3v}**

Figure 2. MP2/6-31G* optimized geometries of the adamantane radical cation ($17^{\bullet+}$) and the transition structure for hydrogen loss from the adamantane radical cation (**22**).

SET Activation of the Tertiary C−H Bond of Adamantane. In contrast to the parent acyclic analogue isobutane, SET oxidation of adamantane leads to a highly delocalized C_{3v}-symmetric radical cation ($\mathbf{17}^{+\bullet}$) with one substantially elongated C−H and three long C−C bonds (Scheme 8 and Figure 2).[86−88] Fragmentation of the tertiary C−H bond, which is partially broken,[89] is preferred, i.e., the adamantane radical cation can lose either a hydrogen or a proton. As expected, in the gas phase the fragmentation of $\mathbf{17}^{+\bullet}$ to the 1-adamantyl cation **18** and a hydrogen atom (Scheme 8) is much more favorable than loss of a proton (+13.8 vs +188.1 kcal mol^{-1}, respectively). The partially broken C−H bond elongates considerably[90] (Figure 2) in the transition structure for hydrogen loss (**22**) and the computed barrier is substantial (16.1 kcal mol^{-1} at MP2/6-311+G**//MP2/6-31G* + ΔZPVE(MP2/6-31G*). The computed KIE for this reaction ($k_H/k_D = 2.0$) is in agreement with our electron impact mass spectrometry (EI-MS) data: Under these conditions adamantane[91] eliminates hydrogen atoms exclusively from the bridgehead positions (the [M−H$^+$] ion is not observed in the EI-MS of 1,3,5,7-tetradeuterioadamantane)

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(84) Klimochkin, J. N.; K., M. I. *Zh. Org. Khim.* **1988**, *24*, 557.

(85) Bach, R. D.; Holubka, J. W.; Badger, R. C.; Rajan, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 4416.

(86) There are some limitations in using isobutane as a model for C−H activation of cage compounds such as adamantane. If electrophilic activation proceeds via similar TSs, the mechanistic picture for oxidation reactions is expected to be quite different. The isobutane radical cation is stable only in C_s symmetry with one elongated C−C bond and shortened C−H bonds: C−C bond fragmentation is favorable. The adamantane radical cation has a stable C_{3v} minimum with a long C−H bond and hydrogen loss occurs as a one-step process.

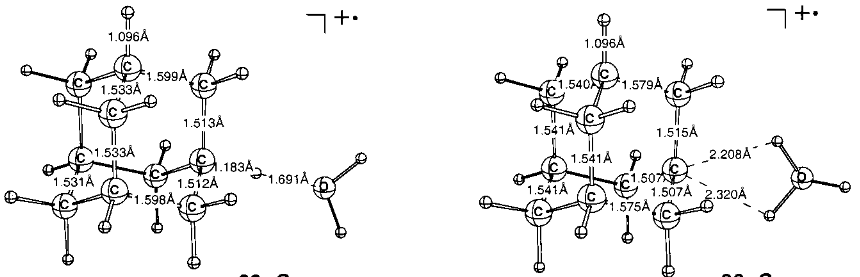
(87) Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1982**, *104*, 5700.

(88) Olivella, S.; Solé, A.; McAdoo, D. J.; Griffin, L. L. *J. Am. Chem. Soc.* **1994**, *116*, 11078.

(89) Toriyama, K.; Nunome, K.; Iwasaki, M. *J. Phys. Chem.* **1986**, *90*, 6836.

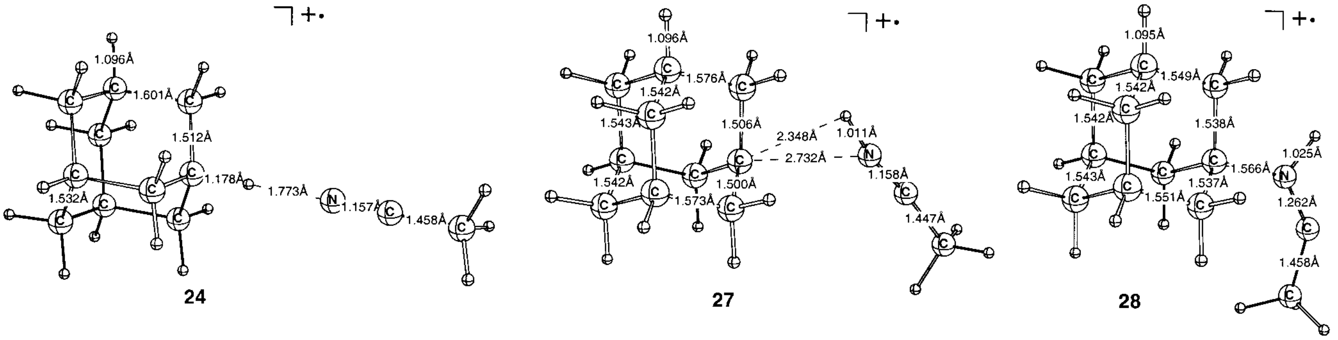
(90) Bally, T.; Sastry, G. N. *J. Phys. Chem. A* **1997**, *101*, 7923.

(91) Bezoari, M. D.; Kovacic, P.; Gadneux, A. R. *Org. Mass Spectrom.* **1996**, *9*, 507.



23, C_1 **26**, C_1

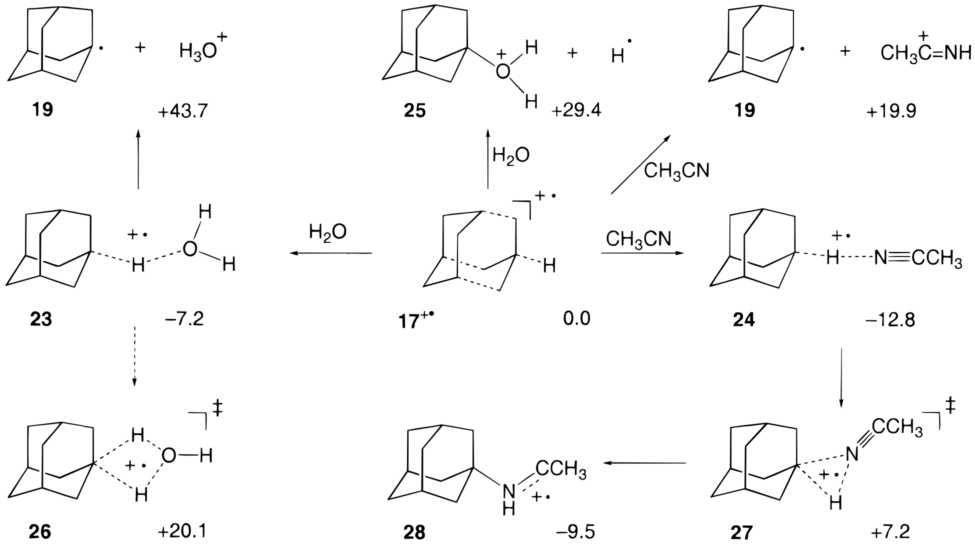
Figure 3. B3LYP/6-31G* optimized geometries of the initial complex (**23**) and the transition structure for hydrogen exchange (**26**) of the adamantane radical cation with H_2O.



24 **27** **28**

Figure 4. B3LYP/6-31G* optimized geometries of the initial complex (**24**) and the transition structure for proton migration (**27**) as well as acetonirtile insertion product (**28**) for the reaction of the adamantane radical cation with CH_3CN.

Scheme 9. Proton Transfer from the Adamantane Radical Cation to Water and Acetonitrile {Relative Energies in kcal mol^{-1} at B3LYP/6-311+G**//B3LYP/6-31G* + ΔZPVE}



and the ratio of [M−H]$^+$ (for adamantane) and [M−D$^+$] (for 1,3,5,7-tetradeuterioadamantane) in the mass spectra reflects the relative rates for the C−H vs C−D bond fragmentation (k_H/k_D = 2.78 ± 0.20)

As mentioned above, proton loss from the adamantane radical cation is energetically highly unfavorable in the gas phase but may readily occur in the condensed state due to the stabilization of the proton.[92,93] We evaluated the structures depicted in Scheme 8 including one (acetonitrile) and up to three explicit solvent molecules (water). The adamantane radical cation forms an initial complex with a water (**23**, Figure 3 and Scheme 9) and with an acetonitrile molecule (**24**, Figure 4 and Scheme 9); the complexation exothermicities are substantial (−7.2 and −12.8 kcal mol^{-1}). The bridgehead C−H bond is elongated considerably in these complexes relative to the unsolvated radical cation **17**$^{+\bullet}$. Proton migration from **17**$^{+\bullet}$ to water (Scheme 9) is +43.7 kcal mol^{-1} endothermic; for acetonitrile this process is less unfavorable (+19.9 kcal mol^{-1}). Although including just one solvent molecule in these computations is a very crude model, it shows that hydrogen loss from the adamantane radical cation with formation of protonated 1-hydroxyadamantane (**25**) is 14.3 kcal mol^{-1} less unfavorable than proton loss. Clearly, these reactions are dominated by the exceptional stability of tertiary 1-adamantyl systems both in the gas phase and in the condensed state. This situation keeps changing until three water molecules are included, at which point the two

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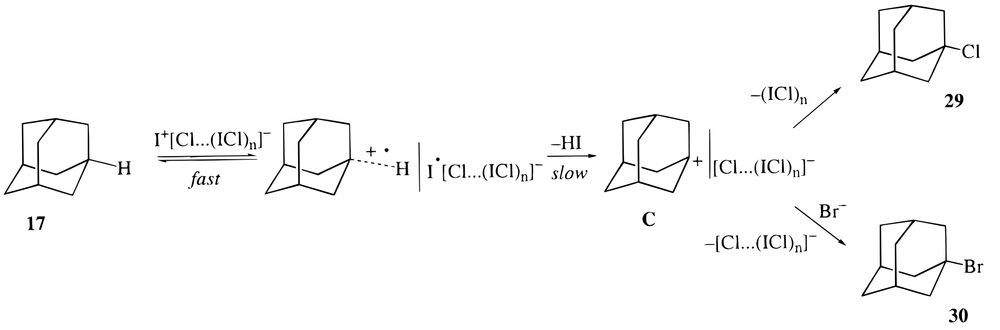
[92] Albini, A.; Mella, M.; Freccero, M. *Tetrahedron* **1994**, *50*, 575.

[93] Lewis, F. D.; Zebrowski, B. E.; Correa, P. E. *J. Am. Chem. Soc.* **1984**, *106*, 187.

Scheme 10. Proposed Mechanism for the SET-Initiated C−H Activation of Adamantane with ICl



reactions, hydrogen (4.9 kcal mol^{-1}) or proton loss (−3.5 kcal mol^{-1}), both become close to thermoneutral.

The transition structure for proton exchange with water (**26**) in the adamantane radical cation (Figure 3) was located; the barrier is 27.3 kcal mol^{-1}. In contrast, transition structure **27** describes insertion of an acetonitrile molecule into the activated C−H bond of the adamantane radical cation via *proton* migration; the geometry of the adamantane moiety in transition structure **27** is similar to that of the 1-adamantyl radical (**19**). The resulting product structure **28** is 3.3 kcal mol^{-1} less stable than the initial complex of acetonitrile with the adamantane radical cation **24**,[94−96] but this energy difference lies well within the error bars of our crude model. As **28** is able to stabilize the radical cation internally through its π-system, the reaction of **17**$^{+\bullet}$ with acetonitrile is much more favorable than the reaction with water.

The proton migration to acetonitrile has a barrier of 20.0 kcal mol^{-1} (via **27**) and the computed KIE for proton loss is small ($k_H/k_D = 1.35$) due to the nonlinear character of the participating bonds in **27** (Figure 4). Such low KIEs were also observed for the elimination of a proton from substituted aromatic radical cations in acetonitrile ($k_H/k_D = 1.0$ in pure CH_3CN and $k_H/k_D = 1.4$ in a 4:1 mixture of CH_2Cl_2/CH_3CN).[97−100]

It appears that only hydrogen atom loss from the adamantane radical cation shows pronounced KIEs which are comparable to those observed experimentally for reactions of adamantane with electrophilic oxidizers (Table 1). This suggests single-electron oxidation steps for these types of reactions, followed by hydrogen atom loss from the radical cation and nucleophilic capture of the carbocation thus formed.

Table 1. Kinetic Isotope Effects for the Reaction of the Bridgehead Adamantane C−H Bond under Various Conditions

reaction of adamantane with	KIE	suggested mode of reaction
$H_3O_2^+$	1.07[a]	hydride abstraction
tert-butyl cation	1.05 ± 0.1	hydride abstraction
HNO_3 (100%)	4.5 ± 0.3[84]	SET
NO^+ and NO_2^+	1.9−2.3[85]	SET
Br_2	3.9 ± 0.2	SET
H loss from radical cation	2.78 ± 0.2[b]	SET follow-up reaction

[a] Computed value at MP2/6/31G*. [b] Computed (MP2/6-31G*) value = 2.0.

On the basis of our findings it is understandable that the halogenations of propellanes **3** and **4** exclusively produce alkyl chlorides. The reaction of adamantane with ICl also leads to 1-*chloro*adamantane **29** as the sole product. Scheme 10 outlines the mechanism we envisage for this reaction based on the evidence presented in the present paper. Reversible SET to ICl[101] is followed by slow hydrogen migration and HI elimination from the radical ion complex; fast carbocation recombination with the nucleophile gives **29**.

To probe the existence of 1-adamantyl intermediates in the course of the halogenation, the reaction of adamantane with ICl was run in the presence of both cation and radical traps. The chlorination with ICl in the 1-position of adamantane in the radical trapping solvent $BrCCl_3$[102,103] proceeds with 98% selectivity. Formation of traces only of 1- and 2-bromoadamantane in a 2:1 ratio is a result of parallel free-radical halogenation with $BrCCl_3$.[104] This clearly indicates that the adamantane radical is *not* formed during the chlorination of adamantane with I^+Cl^-.

The chlorination of adamantane in the presence of Et_3(Dodecyl)N^+Br^- in CCl_4 is accompanied by formation of 20% of 1-bromoadamantane **30** as a result of ion pair **C** capture with Br^- (Scheme 10). The high KIEs for this reaction are strong evidence against the formation of the adamantyl cation as a result of electrophilic hydride abstraction through the halogens.

Conclusions

The present combined experimental/computational study provides strong evidence for oxidative single-electron transfer pathways in the functionalization of aliphatic hydrocarbons with oxidizing electrophiles. While the highly reactive propellanes **1** and **2** react with halogens through a free-radical pathway, the

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(94) Adamantane photooxidation with 1,2,4,5-tetracyanobenzene (TCB) in acetonitrile proceeds with intermediate formation of the adamantyl radical cation; further fragmentation to the 1-adamantyl radical occurs via elimination of a proton. We studied the KIE of this reaction experimentally for competitive adamantane and 1,3,5,7-tetradeuterioadamantane photooxidation using Mella's conditions (ref 96). The observed inverse KIE (0.90 ± 0.05) shows that proton loss is not included into the rate-limiting step. A detailed study will be published elsewhere.

(95) Mella, M.; Fagnoni, M.; Freccero, M.; Fasani, E.; Albini, A. *Chem. Soc. Rev.* **1998**, *27*, 81.

(96) Mella, M.; Freccero, M.; Soldi, T.; Fasani, E.; Albini, A. *J. Org. Chem.* **1996**, *61*, 1413.

(97) An alternative mechanism for the deprotonation of the adamantane radical cation involving fast and reversible formation of **27** and further elimination of CH_3CNH^+ cannot be excluded. Generally, it is difficult to differentiate between two possible ways of proton loss form hydrocarbon radical cations in the presence of a nucleophile, i.e., between direct proton transfer to the nucleophile and nucleophilic addition−elimination reactions.

(98) Masnovi, J. M.; Sankararaman, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2263.

(99) Anne, A.; Fraoua, S.; Hapiot, P.; Moiroux, J.; Savèant, J.-M. *J. Am. Chem. Soc.* **1995**, *117*, 7412.

(100) Parker, V. D.; Chao, Y. T.; Zheng, G. *J. Am. Chem. Soc.* **1997**, *119*, 11390.

(101) Halogenation of adamantane and its derivatives is characterized by high concentrational rate orders in halogen. For the bromination of adamantane the formal reaction order in Br_2 is 6.9; for the chlorination with ICl this value is 3.5.

(102) Cook, G. K.; Mayer, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 1855.

(103) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.

(104) Schreiner, P. R.; Lauenstein, O.; Kolomitsyn, I. V.; Nadi, S.; Fokin, A. A. *Angew. Chem.* **1998**, *110*, 1993; *Angew. Chem., Int. Ed.* **1998**, *37*, 1895..

less reactive hydrocarbons **3** and **4** are oxidized in a stepwise fashion. C−C bond fragmentation of the incipient radical cation leads to strain decrease which is the main driving force for effective σ_{C-C} bond oxidation of strained cyclic systems with relatively stable electrophiles. A similar situation arises for tertiary C−H bond halogenations of adamantane where elimination of a hydrogen atom from the radical cation leads to the relatively stable 1-adamantyl cation.

The KIEs for C−H bond substitution were determined experimentally and computationally to differentiate electrophilic and oxidative activation pathways. Electrophilic hydride abstraction from a tertiary C−H bond of adamantane occurs via an *early* transition structure and displays a low H/D KIE ($k_H/k_D = 1.1$). This is confirmed by similarly low experimental KIEs for the reaction of adamantane and its alkyl-substituted derivatives with the isobutyl cation in the gas phase ($k_H/k_D = 1.05 \pm 0.10$). Proton migration from the hydrocarbon radical cation to the nucleophilic solvent (e.g., CH_3CN) occurs via a *late* transition state, and also displays very low H/D KIEs ($k_H/k_D = 1.0-1.4$).

Hydrogen atom loss from the adamantane radical cation (i.e. formation of the relatively stable 1-adamantyl cation) shows considerably *higher* KIEs. This was studied by means of electron impact ionization techniques ($k_H/k_D = 2.78 \pm 0.20$) and ab initio computations ($k_H/k_D = 2.0$). These KIEs are consistent with experimental data for the reactions of adamantane with electrophilic reagents. The resulting carbocationic intermediates are trapped by nucleophiles leading to the products.

Our results demonstrate and emphasize that the activation of moderately strong C−C and tertiary C−H bonds with elementary halogens or other weak to moderate electrophiles does not follow the traditional electrophilic pathway which involves 3c-2e bonding situations. Instead, single-electron oxidations lead to alkane radical cations which undergo C−C or C−H bond cleavage.

Computational Methods

Geometries were fully optimized at the MP2/6-31G* and B3LYP/6-31G* levels of theory (unrestricted wave functions were used for open-shell species) as implemented in the Gaussian 94[105,106] and Gaussian 98[107] program packages. We utilized two different levels of theory because it is not yet clear which of the two is more appropriate for treating (large) radical cation systems. While MP2 sometimes suffers from spin contamination (our spin operator expectation values ($\langle S^2 \rangle$) were in the range of 0.750−0.763), DFT ($\langle S^2 \rangle = 0.750-0.753$) sometimes does not do well for charge/spin separated systems,[90,108,109] and may suffer from symmetry breaking.[110,111] The positive experience in computing radical cation structures with DFT in other[112−117] and our groups[24,25] favors this approach somewhat. It should be noted that the differences in, for instance, the ZPVEs, between B3LYP and MP2 can be substantial as indicated for $\mathbf{17}^{+\bullet}$. This may be a peculiarity of the degenerate C_{3v} symmetry of this structure but emphasizes that great care must be taken when dealing with radical cations. Additionally, some radical cation structures, such as the TS for loss of a hydrogen from the adamantyl radical cation, could not be located at the DFT level. Structures **23**−**28** could only be optimized at the DFT level due to their considerable size. Single point energies were evaluated utilizing the 6-311+G** basis set. Harmonic vibrational frequencies were computed to ascertain the nature of all stationary points (the number of the imaginary modes, NIMAG, is 0 for minima and 1 for transition structures). All relative energies are corrected for zero-point vibrational energies (ZPVE). Kinetic isotope effects were calculated using the differences in H and D vibrational frequencies as outlined in ref 118.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. NMR spectra were measured on a Varian VXR-300 spectrometer at 300 (^1H NMR) and 75 MHz (^{13}C NMR). Chemical shifts are reported in ppm and are referenced to TMS as internal standard. Routine GC-MS data were obtained using a Hewlett-Packard 5970A/5971A spectrometer (HP GC-MS capillary column 50 m × 0.2 mm, Ultra 1, Silicone, 80−250 °C). Electron impact (EI) (70 eV) and chemical ionization (CI) (isobutane) mass spectra were recorded on a double focusing mass spectrometer Finnigan MAT-8430 with GC inlet (Carlo Erba HRGC-MS, capillary column 30 m × 32 mm, DB-5, 80−300 °C temperature program 6 deg min^{-1}).

Materials. All commercial reagents were ACS reagent grade and were used without further purification. Propellanes **1** and **2** were prepared from 1,3-dibromoadamantane[119] and 1,5-dibromobicyclo[3.3.1]-nonane,[120] respectively, via debromination with Na/K alloy in diethyl ether and then sublimed in vacuo at 30 °C. The original procedure was used for the preparation of 3,6-dihydrohomoadamantane (**3**);[50] [3.3.2]propellane[49] was prepared by photocyclization of 1,5-dimethylenecyclooctane in diethyl ether in the presence of Cu_2I_2. All syntheses were carried out under argon atmosphere.

Reaction of 1,3-dehydroadamantane (1) with ICl: To a solution of 500 mg (3.7 mmol) of **1** in 5 mL of CH_2Cl_2 at 0 °C was added dropwise a solution of 600 mg (3.7 mmol) of ICl in 10 mL of CH_2Cl_2 until the color persisted. The reaction mixture was diluted with aqueous Na_2SO_3. The residue was extracted with CH_2Cl_2 (3 × 10 mL), washed with water, and dried over Na_2SO_4; excess $CH_2Cl_2$was removed. The reaction mixture (930 mg) was analyzed by GC-MS and showed the following main EI peaks:[121] 1,3-diiodoadamantane (**7**, 45%)−388 (1%), 261 (100%), 134 (15%), 91 (20%); 1-chloro-3-iodoadamantane (**5**, 20%)

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(105) *Gaussian 94*, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A., Gaussian, Inc., 1995, Revision E.2.

(106) Foresman, J. B.; Frisch, Æ. *Exploring Chemistry with Electronic Structure Methods*, 2nd. ed.; Gaussian, Inc.: Pittsburgh, 1996.

(107) *Gaussian 98*, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowsk, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., Gaussian Inc., 1998, Version A.5.

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(111) Rauhut, G.; Clark, T. *J. Am. Chem. Soc.* **1993**, *115*, 9127.

(112) Oxgaard, J.; Wiest, O. *J. Am. Chem. Soc.* **1999**, *121*, 11531.

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(114) Laming, G. J.; Handy, N. C.; Amos, R. D. *Mol. Phys.* **1993**, *80*, 1121.

(115) Clark, T. *Top. Curr. Chem.* **1996**, *177*, 1.

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(117) Ma, N. L.; Smith, B. J.; Pople, J. A.; Radom, L. *J. Am. Chem. Soc.* **1991**, *113*, 7903.

(118) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; John Wiley & Sons: New York, 1980.

(119) 1,3-Dibromoadamantane was prepared with 85% yield via bromination of adamantane in the presence of catalytic amounts of $FeBr_3$ under reflux in liquid bromine (Lichotvorik, I. R.; Dovgan', N. L.; Danilenko, G. I. *Zh. Org. Khim.* **1977**, *13*, 897).

(120) 1,5-Dibromobicyclo[3.3.1]nonane was prepared from 1,5-dihydroxybicyclo[3.3.1]nonane (Klimochkin, Yu. N.; Zhilkina, E. O.; Abramov, O. V.; Moiseev, I. K. *Zh. Org. Khim.* **1993**, *29*, 1358) with PBr_3 in CCl_4.

296 (1%, $[M]^{+\bullet}$), 261 (1%), 169 (100%), 133 (50%), 91 (50%); 1,3-dichloradamantane (**6**, 10%)[122] 204 (3%), 169 (100%), 133 (3%), 91 (15%); and several compounds (indicative of a radical process) of low overall yield (5%) formally corresponding to the elemental composition of 1-iodo-(3-chloradamant-1-yl)-adamantane (**8**) 260 (100%), 225 (30%), 169 (60%), 133 (35%), 107 (30%), 91 (20%).

Reaction of [3.3.1]propellane (2) with ICl: From 100 mg (0.82 mmol) of **2** in 1 mL of CH_2Cl_2 with 134 mg (0.83 mmol) of ICl in 2 mL of CH_2Cl_2 according to the above procedure was obtained 195 mg of colorless liquid. Main components of the reaction mixture from GC-MS data: 1-chloro-3-iodobicyclo[3.3.1]nonane (**9**, 25%) 157 (20%), 121 (100%), 93 (60%), 79 (75%), 67 (25%); 1,5-dichlorbicyclo[3.3.1]-nonane[123] (**10**, 25%) 192 (3%), 157 (100%), 121 (85%), 116 (25%), 92 (40%), 79 (58%); 1,5-diiodobicyclo[3.3.1]nonane (**11**, 15%) 249 (1%), 121 (100%), 93 (55%), 79 (70%), 67 (31%); 1-iodo-(5-chlorobicyclo[3.3.1]non-1-yl)bicyclo[3.3.1]nonane (**12**, 17%) 249 (1%), 157 (95%), 121 (100%), 93 (80%), 79 (90%), 68 (30%), 53 (20%).

Reaction of 3,6-dehydrohomoadamantane (4) with ICl: (a) A solution of 180 mg (1.1 mmol) of ICl in 2 mL of CH_2Cl_2 was added dropwise to a solution of 80 mg (0.54 mmol) of **4** in 1 mL of CH_2Cl_2 at 20 °C and the mixture was stirred for 1 h, then diluted with an aqueous solution of Na_2SO_3. The residue was extracted with CH_2Cl_2 (3×5 mL), the extracts were washed with water and dried over Na_2SO_4; excess CH_2Cl_2 was removed. The mixture was filtered through silica (hexane) and 108 mg (0.49 mmol, 90%) of 3,6-dichlorohomoadamantane **14** was obtained. The NMR and IR spectral data for **14** were identical with literature data.[123] (b) From 80 mg of **4**, 180 mg of ICl in 3 mL of $CBrCl_3$ according to procedure a after removing of $BrCCl_3$ in vacuo was obtained 135 mg of a colorless oil. The GC-MS indicated that the reaction mixture contained 67% of **14** (MS and retention time were identical with standard sample) and 15% of 3-bromo-6-chlorohomoadamantane: 227 (1%, $[M]^{+\bullet}$), 183 (100%), 147 (25%), 105 (25%), 91 (44%), 79 (20%), 77 (20%), 39 (28%).

3,6-Dimethoxyhomoadamantane (15): A solution of 2.75 g (16.9 mmol) of ICl in 5 mL of CH_3OH was added dropwisely to a solution of 250 mg (1.69 mmol) of **4** in 5 mL of CH_3OH at 30 °C and the mixture was stirred for 50 h, then quenched with an aqueous solution of Na_2SO_3; CH_3OH was removed in vacuo. The residue was extracted with $HCCl_3$ (3×20 mL), the extract was washed with water and dried over Na_2SO_4, and $HCCl_3$ was removed. The mixture was filtered through silica (ether−hexane 1:2) and 225 mg (63%) of 3,6-dimethoxyhomoadamantane **15** was obtained; ^1H NMR, ^{13}C NMR, and IR spectra were identical with the ones described by Israel and Murray.[124] MS: 210 (5%, $[M]^{+\bullet}$), 179 (20%), 125 (100%), 109 (70%), 91 (22%), 79 (25%), 77 (23%), 55 (23%), 53 (21%). Found: C, 74.15; H, 10.64. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55.

3,6-Diacetaminohomoadamantane (16): A solution of 692 mg (4.26 mmol) of ICl in 3 mL of CH_3CN was added dropwise to a solution of 107 mg (0.72 mmol) of **3** in 5 mL of CH_3CN at 20 °C and the mixture was stirred for 1 h, then diluted with an aqueous solution of Na_2SO_3. The residue was extracted by $HCCl_3$ (3×5 mL), the extract was washed with water and dried over Na_2SO_4, and $HCCl_3$ was removed. The mixture was filtered through silica (ether−methanol 9:1). The spectral data for the 30 mg (15%) of isolated **16** were identical with those described earlier.[23]

Reaction of [3.3.2]propellane (3) with ICl: From 75 mg (0.54 mmol) of **3** and 280 mg of ICl (1.72 mmol) in 3 mL of CH_2Cl_2 following the above procedure for the chlorination of **4** was obtained 108 mg (90%) of 1,5-dichlorobicyclo[3.3.2]decane (**13**). The ^1H NMR spectrum was identical with the one described previously.[125] ^{13}C NMR: 34.99, 40.93, 42.63, 72.30. MS: 171 (15%), 157 (75%), 121 (100%), 93 (63%), 79 (63%), 67 (27%), 53 (24%).

Kinetic isotope effect MS measurements: (a) KIE of hydrogen loss from $17^{+\bullet}$. Kinetic isotope effects of hydrogen loss from the adamantane radical cation were measured for adamantane (AdH_4) and 1,3,5,7-tetradeuterioadamantane (AdD_4) fragmentation upon electron impact ionization. KIEs were calculated as the relative abundance of the $[M - 1]^+$ ion in the MS spectrum of AdH_4 and of $[M - 2]^+$ in the spectrum of AdD_4. The intensities of the ion peaks were corrected for ^{13}C isotope abundance (1.1% of ^{13}C). The KIE for hydrogen loss (2.78 ± 0.20) was calculated from multiple series of MS measurements. **(b) KIE of hydride abstraction from 17.** Isobutane was used as the reagent gas for chemical ionization of AdH_4 and AdD_4. AdD_4 CI mass spectrum corrected to ^{13}C abundance: 140 (90.05%), 139 (101.63%), 138 (85.64%). AdH_4 mass CI-MS corrected to ^{13}C abundance: 136 (15.65%), 135 (110.20%). The fraction of ions resulting from the elimination of secondary hydrogens from adamantane (0.3665) was calculated as $I_{139}/(I_{140} + I_{139} + I_{138})$, where I is the ^{13}C corrected abundance of ions in the CI-MS of AdD_4; the fraction of ions $M-H_{sec}$ for AdH_4 was calculated as $0.3665(I_{136} + I_{135}) = 47.22$. The fraction of the ions $M-H_{tert}$ is $(110.20 - 47.22) = 62.98$. Hence, the statistically corrected hydride abstraction rate from tertiary and secondary positions of adamantane is $(12/4)(62.98/47.22) = 4.00$. The same procedure for the separation of the $M-H_{tert}$ from the $M-H_{sec}$ ion fractions was used for different bridgehead methyl substituted adamantanes and their deuterated counterparts. KIE = 1.05 ± 0.10 was computed as $(I_{M-Htert}/\ I_{M-D})$ in multiple series of CI-MS experiments.

Kinetics of liquid-phase bromination of adamantane: The kinetics of adamantane bromination was studied in Br_2/CCl_4 mixtures (concentrations of Br_2 varied from 9 to 15 M). The reactant and product concentrations were followed by GC. The rate constant for adamantane bromination shows nonlinear dependence of the initial bromine concentrations. The pseudo-first-order rate constants were used for KIE measurements. In a typical kinetic experiment both for adamantane and 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 $k_H = 0.62 \pm 0.03$ s^{-1} and $k_D = 0.159 \pm 0.008$ s^{-1} at 25 °C.

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Supporting Information Available: Tables with absolute energies and *x*,*y*,*z*-coordinates of all computed structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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