Molecule-Induced Alkane Homolysis with Dioxiranes

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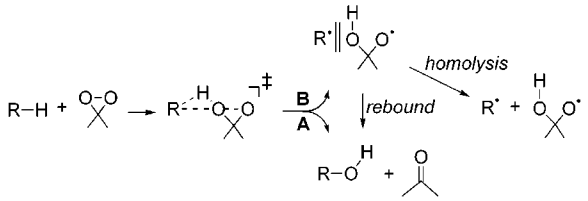
Abstract: The mechanisms of C−H and C−C bond activations with dimethyldioxirane (DMD) were studied experimentally and computationally at the B3LYP/6-311+G**//B3LYP/6-31G* density functional theory level for the propellanes 3,6-dehydrohomoadamantane (**2**) and 1,3-dehydroadamantane (**3**). The σ_{C-C} activation of **3** with DMD ($\Delta G^{\ddagger} = 23.9$ kcal mol^{-1} and $\Delta G_r = -5.4$ kcal mol^{-1}) is the first example of a molecule-induced homolytic C−C bond cleavage. The C−H bond hydroxylation observed for **2** is highly exergonic ($\Delta G_r = -74.4$ kcal mol^{-1}) and follows a concerted pathway ($\Delta G^{\ddagger} = 34.8$ kcal mol^{-1}), in contrast to its *endergonic* molecule-induced homolysis ($\Delta G^{\ddagger} = 28.8$ kcal mol^{-1} and $\Delta G_r = +9.2$ kcal mol^{-1}). The reactivities of **2** and **3** with CrO_2Cl_2, which follow a molecule-induced homolytic activation mechanism, parallel the DMD results only for highly reactive **3**, but differ considerably for more stable propellanes such as 4-phenyl-3,6-dehydrohomoadamantane (**1**) and **2**.

Introduction

Highly reactive three-membered ring peroxides, i.e., dioxiranes, are able to hydroxylate unactivated C−H bonds in aliphatic hydrocarbons under mild conditions[1−3] with remarkably high tertiary/secondary positional selectivities, high stereoselectivities, and in good preparative yields.[4−9] Relatively stable dimethyldioxirane (DMD) is one of the key reagents for alkane oxidations which can easily be prepared from acetone and $[(KHSO_5)_2{\cdot}KHSO_4{\cdot}K_2SO_4]$.[10] Despite a number of efforts, the mechanism for the C−H activation step is not entirely clear, as there is evidence for both radical[11−13] and nonradical[14−17] pathways. A number of puzzling and controversial experimental results first were rationalized[18] in terms of a bifurcation of the reaction path (Scheme 1) which involves either concerted insertion (A) giving hydroxy products directly,[16] or a radical pair (B) via a *common* transition structure: The bifurcation point is located about 2 kcal mol^{-1} below and *after* the transition structure. Radical pairs thus formed either recombine (rebound)[11] or escape from the solvent cage, giving rise to free radicals (molecule-induced homolysis).[12]

Scheme 1. Bifurcation of the Reaction Pathway in the C−H Bond Activation with DMD



The mechanistic dichotomy in the reactions of DMD with alkanes also may arise from the potential multistate reactivity[19] of DMD. The closed-shell $^1A_1$ singlet ground state is only 11.5 kcal mol^{-1} more stable than the biradical open-shell OS-$^1A_1$ singlet state at B3LYP/6-311+G**//B3LYP/6-31G* and 11.1 kcal mol^{-1} at CCSD(T)/VTZ2P+f,d.[20] Computations show that three distinctly different pathways on the singlet PES could take place, as shown in Scheme 2 for the reaction of DMD with isobutane. Insertion of $^1A_1$-DMD into a C−H bond occurs in a concerted fashion (**TS1**) as found by a number of groups.[21−23]

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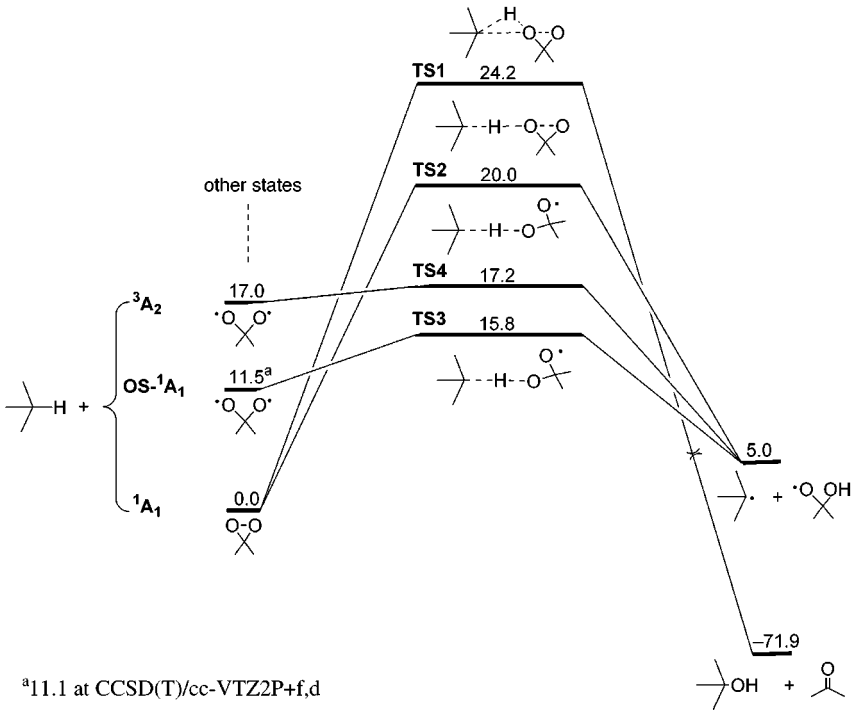
Scheme 2. Possible Reaction Pathways for the Isobutane/DMD System Computed at B3LYP/6-311+G**//B3LYP/6-31G* (ΔE, kcal mol^{-1})[a]



[a] These data are compiled from our own computations and from the respective literature.[21,23]

The barrier for this reaction at B3LYP/6-311+G**//B3LYP/6-31G* is 24.2 kcal mol^{-1}. The H-abstraction via linear **TS2** with formation of the radical pair exemplifies the molecule-induced homolytic pathway.[23] While it is accompanied by a lower barrier (20.0 kcal mol^{-1}), this reaction is endothermic; this low-barrier reaction could, however, be driven by the exothermic radical recombination or other transformations of the two incipient products. The barrier for the radical reaction with OS-$^1A_1$-DMD is even lower (**TS3**, 15.8 kcal mol^{-1}) and may also lead to radical pair formation, although this pathway is hampered by the high *barrier* for DMD homolysis (OS-$^1A_1$-DMD is the product of this process); the O−O bond breaking requires an activation of 23.0 kcal mol^{-1} at CCSD(T)/cc-VTZ2P+f,d,[20] and 23.1 kcal mol^{-1} at B3LYP/6-31G**.[20] H-abstraction can also occur on the ground-state triplet surface: The $^3A_2$-DMD biradical lies 5.5 kcal mol^{-1} above OS-$^1A_1$-DMD, and H-abstraction with $^3A_2$-DMD via **TS4** forming the radical pair is virtually barrierless.

Dioxiranes are also characterized by a number of low-lying exited states[24] which may participate in the C−H activation reactions; these channels are supported by recent observation of weak chemiluminescence in the reaction of certain dioxiranes with hydrocarbons (for instance, with the significantly more reactive methyl(trifluoromethyl)dioxirane, TDA, reacting with adamantane).[25] Thus, the activation of C−H bonds with DMD is indeed very complex: traces of radical starters may cause free-radical processes, and depending on the reaction media, as well as the structure of the hydrocarbon, different reaction pathways may be followed. Hypersensitive radical clocks with rearrangement times close to the lifetime of the transition states[16,17] do not support free-radical pathways but leave the question of concerted vs molecule-induced homolytic/rebound mechanism unanswered.

It should be emphasized that the mechanisms giving open-shell species (i.e., molecule-induced homolysis) from closed-shell reactants are rare.[26] This scenario is, however, typical for alkane activations utilizing metal−oxo reagents where two radicals can form from the reaction of two closed-shell molecules. Concerted insertion[27−30] vs hydrogen abstraction/rebound[31−33] as well as molecule-induced homolytic[31,34] mechanisms are discussed vividly; the reactivity of CrO_2Cl_2 is most well studied,[34−38] and a molecule-induced homolytic mechanism was unequivocally shown for the C−H activation step.[36,37]

Although there are some obvious common experimental findings in alkane activations with dioxiranes and metal−oxo species (high tertiary selectivities, stereoselectivities, and sensitivity to radical traps), this connection has been made only vaguely, and there are no decisive mechanistic comparisons.[32] This is mostly due to the lack of relevant model hydrocarbons that are able to distinguish the mechanistic steps cleanly. In the present paper we describe the preparative transformations of three well-chosen strained propellanes (**1**−**3**) which allow us

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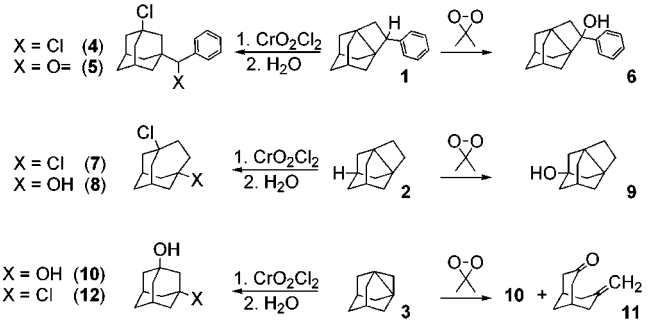
Scheme 3. Experimental Results on the Reactions of Propellanes **1**−**3** with DMD and CrO_2Cl_2



to study the competition between the C−H and the C−C bond activations in the reactions with DMD and CrO_2Cl_2 and verify the differences in their reactivities. These investigations also reveal important mechanistic aspects of the reactions of aliphatics with uncharged closed-shell electrophiles, in particular with DMD.

Results and Discussion

As the ring size controls their strain and thus their reactivity, propellanes[39] (in particular, **1**−**3**[40,41]) have proven to be relevant and highly valuable substrates in our[42−48] and other[49,50] groups for modeling alkane activation mechanisms. Our results for the reactions of **1**−**3** with DMD and CrO_2Cl_2 are summarized in Scheme 3. These reactions were run at low conversions to avoid side reactions (see Experimental Section for details).

In the reactions of **1** and **2**[44] with CrO_2Cl_2, we only found C−C bond *addition* products (**4**, **5**, **7**, and **8**), while the transformations with DMD exclusively give C−H *substitution* products (**6** and **9**). At the same time, **3** forms only C−C addition products with both DMD and CrO_2Cl_2. Dihydroxy derivative **10** is produced with both DMD and CrO_2Cl_2, while cage fragmentation product **11** is isolated from the reaction of **3** with DMD; conversely, chlorohydroxy product **12** forms with CrO_2Cl_2. The cage fragmentation is in marked contrast to the addition reactions previously found for the reactions of **3** with a number of radical reagents such as halogens,[51] halomethanes, and oxygen;[52] radical oligomerizations dominate in the latter case.

The reactivity difference of **1** and **2** toward DMD is not surprising because the benzylic hydrogen is more reactive relative to pure aliphatics.[53] The cage isomerization of **1** upon treatment with CrO_2Cl_2 is very similar to the rearrangement of 4-substituted 3,6-dehydrohomoadamantanes in its reactions with electrophiles/oxidizers.[43] The oxidation of **3** is the first example of an alkane σ_{C-C} bond activation with dioxirane. Nonetheless, this is *not* observed for **2**, although both hydrocarbons are highly strained (vide infra). To elucidate the mechanistic details and the nature of such apparent reactivity differences, we studied certain aspects of these reactions computationally (Table 1, Supporting Information; see Computational Methods for details) at the B3LYP/6-311+G**//B3LYP/6-31G* level of theory (Scheme 4).

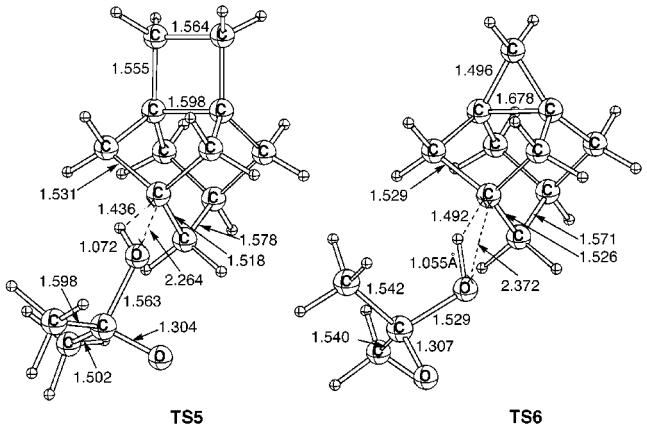


Figure 1. B3LYP/6-31G* optimized geometries for the transition structures **TS5** and **TS6** (selected bond distances in angstroms).

Transition structures **TS5** and **TS6** (Figure 1) for the C−H activation of **2** and **3**, respectively, describe the insertion of the oxygen into the C−H bonds; the $\Delta G_{298}^{\ddagger}$ values are similar (34.8 and 30.5 kcal mol^{-1}) for both hydrocarbons. These highly exergonic ($\Delta G_{298} = -74.4$ and -75.2 kcal mol^{-1}) insertions occur as one-step concerted processes terminating with alcohols **9** and **13** after acetone elimination, respectively. Although the barrier for H-abstraction with DMD on the open-shell singlet manifold is lower (28.7 kcal mol^{-1}) than for the concerted insertion, dissociation into the radical **14** is *endergonic* (9.2 kcal mol^{-1}) and cannot effectively compete with the concerted hydroxylations. However, this does not rule out fast radical recombination which may be exothermic. The activation enthalpies for the concerted insertions via **TS5** and **TS6** ($\Delta H^{\ddagger} = 27.4$ and 22.3 kcal mol^{-1}, respectively) are very close to those computed previously[21,23] for the activation of the tertiary C−H bond of isobutane in its reaction with DMD (24.2 kcal mol^{-1}, **TS1**, Scheme 2). Thus, the experimentally observed hydroxylation of the C−H bond of propellane **2** is likely to occur via a nonradical concerted pathway; molecule-induced homolysis is thermodynamically unfavorable.

While the similarities of the computational results obtained for the C−H hydroxylations of **2** and **3** are not surprising, the reactivities of their C−C bonds toward DMD are distinctly different. The addition of DMD to the C−C bond of **2** resulting in biradical **15** is exergonic (−6.8 kcal mol^{-1}) and is accompanied by a high barrier (51.8 kcal mol^{-1}, **TS7**, Figure 2); the alternative barrier for C−H hydroxylation via **TS5** is 17.0 kcal mol^{-1} lower, and this path is highly exergonic (−74.4 kcal mol^{-1}), which agrees well with our experiments (Scheme 3). The reactivity of the C−C vs C−H bonds of **3** toward DMD is quite different: Formation of biradical **16** occurs via low-lying **TS8** ($\Delta G_{298}^{\ddagger} = 23.9$ kcal mol^{-1}) and is −5.4 kcal mol^{-1}

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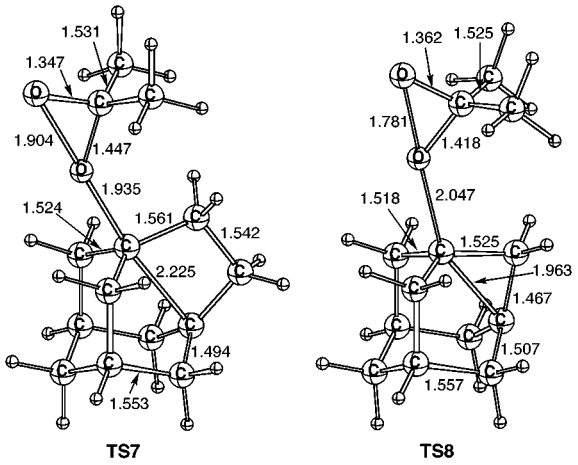
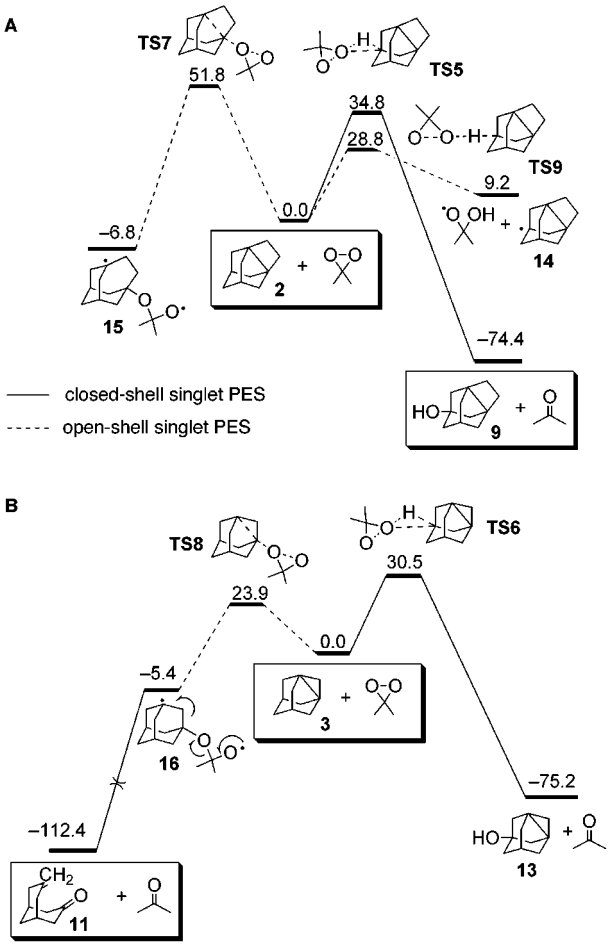


Figure 2. B3LYP/6-31G* optimized geometries for the transition structures **TS7** and **TS8** (selected bond distances in angstroms).

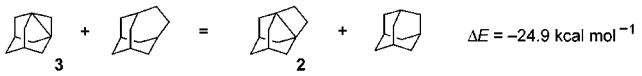
Scheme 4. B3LYP/6-311+G**//B3LYP/6-31G* Computed Pathways (ΔG_{298}, kcal mol^{-1}) for the Reactions of Propellanes **2** (A) and **3** (B) with DMD



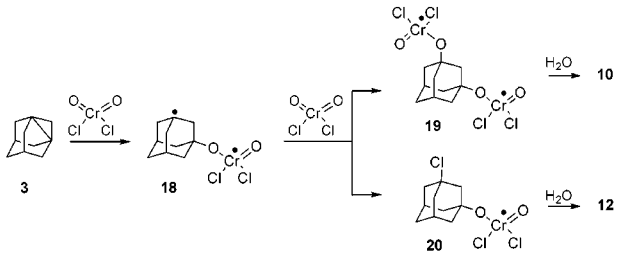
exergonic. In stark contrast to **2**, propellane **3** *can* form biradical **16** easily. This is the first clear-cut example for molecule-induced alkane C−C bond homolysis with DMD. The elimination of acetone from **16** is facile as it does not require much atomic movement (consequently, the exothermicity is extraordinarily high), but merely electron rearrangements as indicated by the half-arrows on **16** in Scheme 4.

The computations nicely complement our experiments (see details below). Despite highly exergonic fragmentation of biradical **16** to ketone **11**, some (8%) dihydroxy product (**10**) forms. The latter can only result from capture of **16** with DMD, which is an efficient radical trap.[34] Note that the strain energy of hydrocarbon **3** is not very much higher than that of **2** (41.1 kcal mol^{-1} for **2** vs 55.5 kcal mol^{-1} for **3**),[45] and strain release in **TS8 vs TS7** cannot be the only reason for such pronounced reactivity differences. A possible explanation is the difference in the propellanic C−C bonds of these hydrocarbons. In contrast to **2**, the quaternary carbons in **3** are inverted,[52] and the central C−C bond has some biradical character. We estimated this through the differences in singlet−triplet energies ($\Delta\Delta E_{ST} = 8$ kcal mol^{-1}) which are much lower for **3** (30 kcal mol^{-1}) than for **2** (42 kcal mol^{-1}, B3LYP/6-31G*) and via the homodesmic equation (Scheme 5), which shows that **3** is 24.9 kcal mol^{-1} less stable (and thus more reactive) than **2**, assuming that adamantane and homoadamantane both have low strain energies.[54] Thus, both computational and experimental results show that molecule-induced homolysis of DMD is possible only for very weak σ-bonds (like in **3**).

Scheme 5. Isodesmic Equation To Evaluate the Relative Reactivities of the Propellanes **2** and **3** at B3LYP/6-311+G**//B3LYP/6-31G*



Scheme 6. Molecule-Induced C−C Bond Homolysis of Propellane **3** with CrO_2Cl_2



On the basis of the experimentally found product distribution for the reaction of **3** with CrO_2Cl_2, the molecule-induced homolysis also seems operative in this case (Scheme 6). Biradical **18** formed after the activation step (Cr^V alkoxides are well-characterized intermediates[55]) could be trapped either by the Cr=O group or through Cl-abstraction from CrO_2Cl_2, giving alkoxides **19** and **20** and alcohols **10** and **12** after aqueous workup. Dihydroxy derivative **10** was found in the reaction of **3** with DMD (vide supra) through an analogous radical trapping reaction of **16**.

Conclusions

The competitive C−H and C−C bond reactivities with DMD, verifying concerted vs homolytic reaction mechanisms, were studied experimentally and computationally for a set of propellanes. Although the molecule-induced homolytic C−H reaction is generally characterized by a slightly lower barrier than the concerted insertion, only the latter reaction is exergonic. The C−C bond addition of DMD is more favorable than the C−H insertion (the $\Delta G_{298}^{\ddagger}$ values are 23.9 vs 30.5 kcal mol^{-1}, respectively) only for highly reactive propellane **3** with an inverted geometry at the quaternary carbons. The molecule-induced homolytic mechanism was also found experimentally for propellanes **1**−**3** in their reactions with CrO_2Cl_2. The reactivities of propellanes **1** and **2** toward DMD (C−H activa-

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tion) and CrO_2Cl_2 (C−C activation) are clearly different, and only relatively unstable **3** reacts with both CrO_2Cl_2 and DMD similarly via thermodynamically favored C−C bond molecule-induced homolysis. Hence, this mechanism, which is typical for metal−oxo reagents in general, and for CrO_2Cl_2 in particular, plays at best a minor role in alkane activations with dioxiranes. In stark contrast to the reactions with metal−oxo reagents, only very weak σ-bonds (like the central C−C bond in **3**) can be homolyzed by ground-state singlet DMD.

Computational Methods

Geometries were fully optimized utilizing the density functional three-parameter hybrid B3LYP functional[56,57] in conjunction with 6-31G* and 6-311+G** basis sets as implemented in Gaussian 98.[58] Temperature corrections (298 K) were derived from B3LYP/6-31G* frequency computations; these corrections were used to correct the higher quality single-point energies at B3LYP/6-311+G**. The "guess=mix" option was used for open-shell singlet state computations. While this is an approximate treatment, others[59,60] and we[61] have had very positive experience with this type of approach; notably, Bach et al. observed RHF→UHF instabilities for some dioxirane structures.[21] Although DFT is, in principle, a single-determinant method, very often obvious multireference states can be described adequately *if* one dominant configuration yields an acceptable density.[20] Hence, the results of such DFT computations must be gauged against higher level methods. As the state splittings for DMD agree well at MRD-CI, CCSD(T), and B3LYP levels of theory, the approach used here seems justified for making qualitative arguments and comparisons with experiment.[22] The reaction pathways along both directions from the transition structures were followed by the IRC method.[62] *xyz* coordinates and energies for all optimized species are summarized in the Supporting Information.

Experimental Section

A. Reaction of 1 with DMD. Into a degassed solution of 312 mg (1.39 mmol) of 4-phenyl-3,6-dehydrohomoadamantane (**1**) in 3 mL of dry acetone was added 21 mL of a 0.073 M acetone solution of DMD (1.54 mmol) under argon. After 20 h the solvents were removed under reduced pressure. Column chromatography (silica gel Merck 60, ether:*n*-hexane = 2:1) of the residue gave 180 mg of unreacted **1** (conversion 42%) and 77 mg (0.32 mmol, 23%) of 4-hydroxy-4-phenyl-3,6-dehydrohomoadamantane (**6**). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.30−1.78 m (7H), 1.86 s (2H), 2.13 AB (15 Hz, 1H), 2.24 bs (2H), 2.47 bs (1H), 2.34 m (1H), 2.77 AB (15 Hz, 1H), 7.25−7.38 (5H). ^{13}C NMR (δ, ppm, $CDCl_3$): 145.25, 128.27, 127.02, 126.64, 76.20, 58.56, 49.66, 49.15, 46.59, 42.40, 42.36, 42.23, 41.59, 41.14, 35.81. MS (70 eV): m/z = 240, 222, 197, 183, 179, 167, 147, 129, 105, 91, 77, 65, 51. Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.05; H, 8.26.

B. Reaction of 2 with DMD. Following procedure A, to 300 mg (2.03 mmol) of 3,6-dehydrohomoadamantane (**2**) in 2 mL of acetone was added 44 mL of a 0.047 M acetone solution of DMD (2.07 mmol), to give 270 mg of unreacted **2** and 20 mg (0.12 mmol, 6%) of 1-hydroxy-3,6-dehydrohomoadamantane (**9**), mp = 171−172 °C. ^{1}H NMR (δ, ppm, $CDCl_3$): 1.55−1.62 m (4H), 1.64−1.70 s (4H), 1.79−1.86 m (1H), 1.88−2.00 m (4H), 2.01−2.08 d (2H), 2.39 bs (1H). ^{13}C NMR (δ, ppm, $CDCl_3$): 80.03, 54.88, 48.01, 46.82, 42.87, 39.30, 28.37. MS (70 eV): m/z = 164, 146, 136, 121, 109, 106, 95, 91, 81, 67, 55. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.29; H, 9.71.

C. Reaction of 1 with CrO_2Cl_2. Into a stirred solution of 400 mg (1.79 mmol) of **1** in 11 mL of CCl_4 was added a solution of 1.08 g of CrO_2Cl_2 (7.01 mmol) in 10 mL of CCl_4 dropwise at 0 °C under argon. The reaction mixture was quenched with aqueous saturated $Na_2S_2O_5$, the organic layer was separated, and the aqueous part was extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with water and brine and were dried over Na_2SO_4. After removal of the solvent, column chromatography (ether:*n*-hexane = 2:1) of the residue gave 113 mg (0.38 mmol, 21%) of 1-chloro-3-(1-chlorobenzyl)adamantane (**4**) and 366 mg (1.33 mmol, 75%) of phenyl-3-chloroadamant-1-yl ketone (**5**).

Compound 4. ^{1}H NMR (δ, ppm, $CDCl_3$): 1.1−2.3 m (14H), 4.3 s (1H), 7.15 m (5H). ^{13}C NMR (δ, ppm, $CDCl_3$): 137.61, 128.82, 128.06, 127.77, 77.32, 68.32, 48.48, 46.73, 42.36, 37.34, 37.12, 34.59, 31.11. Anal. Calcd for $C_{17}H_{20}Cl_2$: C, 69.16; H, 6.83; Cl, 24.02. Found: C, 69.23; H, 6.81; Cl, 24.13.

Compound 5. ^{1}H NMR (δ, ppm, $CDCl_3$): 7.76 m (1H), 7.53 m (1H), 7.30 m (3H), 2.70 s (2H), 2.33 s (2H), 2.12−2.15 m (2H), 1.7−1.92 m (8H). ^{13}C NMR (δ, ppm, $CDCl_3$): 200.66, 150.32, 133.56, 132.39, 126.73, 126.18, 125.62, 52.12, 51.32, 49.33, 46.63, 45.09, 35.99, 33.56. Anal. Calcd for $C_{17}H_{19}ClO$: C, 74.31; H, 6.97; Cl, 12.90. Found: C, 74.24; H, 6.95; Cl, 12.82.

D. Reaction of 3 with DMD. Following procedure A, from 105 mg (0.78 mmol) of 1,3-dehydroadamantane (**3**) in 10 mL of CH_2Cl_2 and 12.5 mL of a 0.063 M acetone solution of DMD (0.79 mmol) were obtained 55 mg of 3-methylenebicyclo[3.3.1]nonan-7-one (**11**) (0.36 mmol, 46%) and 11 mg of 1,3-dihydroxyadamantane (**10**) (0.06 mmol, 8%), identical from MS and NMR data to standard samples.[63,64] The conversion of **3** was virtually complete as determined after quenching the reaction mixture with water (only trace amounts of 1-hydroxyadamantane as a result of the addition of water to **3** were found). In a series of control experiments, we also ran this reaction with only 10% DMD under argon. After quenching of the reaction with water, the conversion of **3** was found to be close to 10%; the product distributions were identical. Running this reaction in the presence of oxygen (bubbled through the solution), we obtained the same results as under argon in the absence of oxygen. Hence, **3** reacts much faster with DMD than with oxygen, in contrast to the slow reactions of **1** and **2** where DMD decomposes much faster relative to the hydrocarbon oxidation reaction.

E. Reaction of 3 with CrO_2Cl_2. Following procedure C, from 500 mg (3.73 mmol) of **3** in 15 mL of CH_2Cl_2 and a solution of 700 mg of CrO_2Cl_2 (4.52 mmol) in 5 mL of CCl_4 was obtained 445 mg (2.39 mmol, 64%) of 1-chloro-3-hydroxyadamantane (**12**) after column chromatography, identical to the standard sample[65] from MS and NMR data. Changing the solvent to methanol gave 150 mg (0.89 mmol, 24%) of 1,3-dihydroxyadamantane (**10**), also identical to the standard sample.[64]

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Supporting Information Available: *xyz* coordinates and absolute energies (Table 1) of all optimized species (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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