Oxidation of some cage hydrocarbons by dioxiranes. Nature of the transition structure for the reaction of C–H bonds with dimethyldioxirane: a comparison of B3PW91 density functional theory with experiment†

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Dimethyl- (DMD) and methyl(trifluoromethyl)-dioxiranes were used for oxyfunctionalization of spiro{1′,7-cyclopropan-(*E*)-2-methylbicyclo[2.2.1]heptane} (**1**), tricyclo[3.2.2.0^{2,4}]nonane (**2**), *exo-endo-endo*- (**3**) and *exo-exo-exo*- (**4**) heptacyclo[9.3.1.0^{2,10}.0^{3,8}.0^{4,6}.0^{5,9}.0^{12,14}]pentadecane, yielding tertiary alcohols as the main products. The rate constants for oxidation of **1–4** by DMD were measured and the Arrhenius parameters determined. The DFT theory (B3LYP and B3PW91) using restricted and unrestricted methods was employed to study the oxidation reaction of the C–H bond of cage hydrocarbons **1–4**, adamantane, and acetone with DMD. The kinetic isotopic effect calculated using unrestricted methods agreed with experiment. The reaction mechanism in terms of the concerted oxygen insertion *vs.* the radical part is discussed.

Introduction

Norbornane derivatives and their dimers find applications in the production of high-energy multi-purpose rocket fuels.[1] Consequently, the study of their oxidative stability and improvement of fuel characteristics is currently of practical interest in rocket technology. The biological activity of hydroxyl- and oxy-derivatives of cage hydrocarbons represents another important area of application.[2]

The oxidation of hydrocarbons at ambient temperature is a continuing challenge.[3,4] For more than two decades, dioxiranes have been employed for the oxyfunctionalization of various organic substrates with high regio- and stereoselectivity.[5] Despite the amount of work devoted to this problem, the mechanism of oxidation of the C–H bond is still of great interest due to its complexity.[3–7]

The products of the reaction between dimethyldioxirane (DMD) and alkyl- as well as bicyclic derivatives of cyclopropane have been studied in a series of papers and the oxidation of the α-position to the 3-membered ring discussed.[7–9] A similar behavior was found in oxidation reactions of strained polycyclic hydrocarbons, such as binor-S.[10,11] In some cases, however, as in the case of spiro(cyclopropane-1,2′-adamantane),[10] the oxidation occurs at positions remote from the 3-membered ring. A product analysis after reacting methyl(trifluoromethyl)dioxirane (TFD) with 2,4-didehydroadamantane, spiro(cyclopropane-1,2′-adamantane), *n*-butyl cyclopropane, 1-cyclopropyl-3-methylbutane and bicyclo[6.1.0]nonane shows that in most cases the tertiary C–H bonds undergo oxidation, with the exception of 2,4-didehydroadamantane,[10] where the authors reported the relevance of reactivity to the spatial orientation of the cyclopropane moiety and the proximal C–H bond, which is oxidized. In this particular case a cyclopropane moiety, constrained to a favorable "bisected" arrangement, can activate the α-methylene moiety and thus facilitate the oxyfunctionalization of this position, which competes effectively with O-insertion into the other C–H bonds,[10] where oxidation by dioxirane predominantly occurs at the tertiary C–H bonds rather than at secondary or primary ones.[10,11] On the contrary, upon oxidation of spiro(cyclopropane-1,2′-adamantane) by dioxirane, even the bridgehead tertiary C–H bonds become deactivated by the cyclopropyl moiety, lying in an unfavourable perpendicular orientation.[10] Oxidation of propellanes, such as 4-phenyl-3,6-dehydrohomoadamantane and 3,6-dehydrohomoadamantane, by DMD resulted in formation of the corresponding 1- and 4-hydroxy derivatives.[12] Moreover, the thermodynamically favourable molecule-induced homolysis of the C–C bond in the reaction of the relatively unstable 1,3-dehydroadamantane with DMD yields 3-methylenebicyclo[3.3.1]nonan-7-one (46%) and 1,3-dihydroxyadamantane (8%).[12]

The high reactivity of TFD is responsible for the observation of more than one oxidation product in most cases.[6] It is important to mention that even under low temperature reaction conditions (below 0 °C), the products of a radical reaction were not detected for TFD,[5–7,10] whereas the reactions using DMD show the presence of the radical channel (proposed by Minisci *et al.*) in the oxidation of various substrates.[12–15]

The dioxiranes can generate free radicals during reaction with C–H bonds, as proposed in theoretical studies,[12,16,17] and demonstrated by experiment.[9,12–15,18] The results show the possibility of

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Table 1 Conversion of the substrates and yield of alcohols **1a–4a** in the reaction of cage hydrocarbons **1–4** with DMD (in CCl_4; 20 °C) and with TFD (in TFP, 0 °C) after the complete consumption of the dioxiranes

Compound	Oxidant	Conversion[a] (%)	Yield of alcohol[a] (%)
1	DMD	39 (92)	87 (88)
	TFD	99	99
2	DMD	31 (91)	68 (67)
	TFD	99	99
3	DMD	97 (97)	98 (98)
	TFD	99	99
4	DMD	62 (95)	95 (94)
	TFD	99 (92)	98 (88)

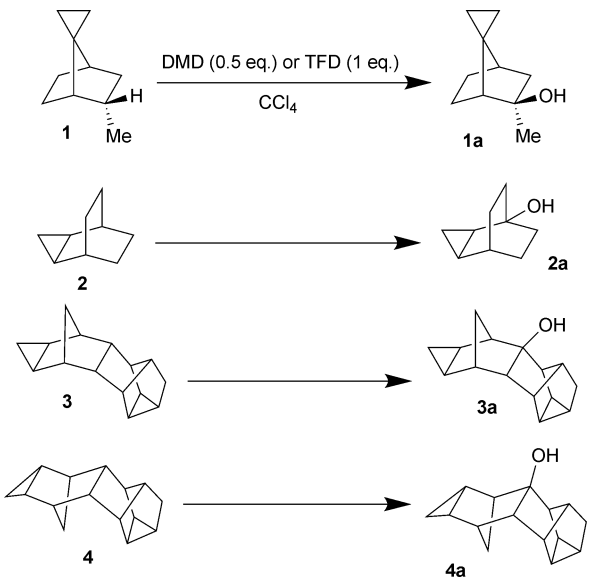
[a] Values in parentheses correspond to the solution saturated with oxygen.

both molecular[5–8,19] and radical mechanisms[3,12–15,18] as a concerted molecule-induced homolytic/rebound process. The contribution of these channels is predominantly determined by the structure of the reactants and the reaction medium.[3,12–15,18]

Here we report the oxidation by DMD and TFD of several norbornane derivatives and tricyclo[3.2.2.$0^{2,4}$]nonane. The mechanism of the oxidation reaction is discussed in terms of concerted oxygen insertion and the possible radical channel.

Results and discussion

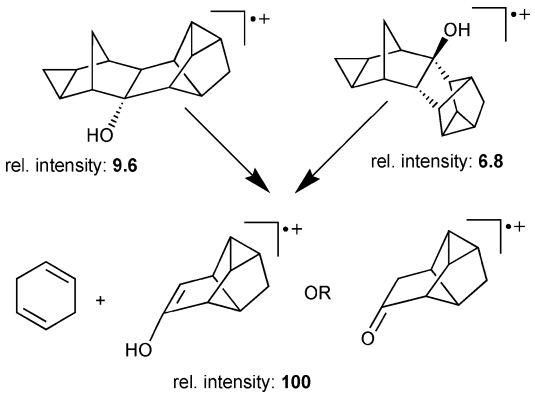
We have found that the oxidation of spiro{cyclopropan-1′,7-(*E*)-2-methylbicyclo[2.2.1]heptane} (**1**), tricyclo[3.2.2.$0^{2,4}$]nonane (**2**), *exo-endo-endo*- (**3**) and *exo-exo-exo*- (**4**) isomers of heptacyclo[9.3.1.$0^{2,10}$.$0^{3,8}$.$0^{4,6}$.$0^{5,9}$.$0^{12,14}$]pentadecane by DMD and TFD in equimolar ratio gives corresponding ternary alcohols with good yields (Table 1). The positions of oxygen insertion are shown in Scheme 1.



Scheme 1

Spectroscopic studies were carried out on the products of the reaction of DMD and TFD with the substrates mentioned above. Along with the IR spectra of alcohols **1a–4a**, which show a strong O–H stretching absorption, varying over 3432–3268 cm^{-1}, analysis of the two-dimensional NMR spectra confirmed the formation of the corresponding alcohols. The electron impact mass spectra give the formulae $C_{10}H_{16}O$ (m/z = 152 by GC-MS) for **1a**, $C_9H_{14}O$ (m/z = 138.105 by HRMS) for **2a**, and $C_{15}H_{18}O$ (m/z = 214.134 and 214.136 by HRMS) for **3a** and **4a** respectively. The protons of the methyl group of product **1a** (Scheme 1) appear as a singlet in the ^{1}H NMR spectra contrary to the products of oxidation of hydrocarbons **2–4**, for which both ^{1}H and ^{13}C NMR spectra show the absence of symmetry elements in products **2a–4a**. The experimental ^{13}C NMR spectra for substrates **1–4** and corresponding alcohols **1a–4a** are in very good agreement (correlation coefficient $r^2 = 0.998$) with the calculated ^{13}C isotropic chemical shifts (Fig. S1, ESI†), computed using the methodology of Vikić-Topić and Pejov.[20] The results of these calculations are included as supporting information.†

The oxidation of *exo-endo-endo*- (**3**) and *exo-exo-exo*- (**4**) isomers of heptacyclo[9.3.1.$0^{2,10}$.$0^{3,8}$.$0^{4,6}$.$0^{5,9}$.$0^{12,14}$]pentadecane by DMD and TFD occurs at the C(2)–H bond (Table 1 and Scheme 1) and independently of the *-endo-endo-* or *-exo-exo-* configuration. The mass spectra of compounds **3a** and **4a** have identical ions, which is characteristic for geometrical isomers.[21] The dissociation of these radical-cations of **3a** and **4a**, leading to the formation of the most abundant fragment ion is shown in Scheme 2.



Scheme 2

Molecular ion fragmentation occurs through cleavage of the C(1)–C(2) and C(10)–C(11) bonds, specific for norbornane radical cation formation.[22] The relative intensity of the molecular ions formed from **3a** and **4a** is 6.8 and 9.6 respectively (Scheme 2). The higher stability of the radical-cation formed from **4a** can be explained due to its smaller strain energy (E_{str}). This is supported by the quantum chemical calculations at the B3PW91/6-311 + G(d,p) level of theory, where the difference between the strained energies of alcohols **3a** and **4a** $\Delta(E_{total}(\mathbf{3a}) - E_{total}(\mathbf{4a}))$ was found to be 4.4 kcal mol^{-1}.

The kinetics of the oxidation of **1–4** by DMD were studied by monitoring consumption of the oxidant, with or without constant oxygen saturation. The kinetic curves have a break which separates two regions with low and high rate correspondingly (see Fig. 1), as previously demonstrated in the oxidation of other alkanes, including adamantane (**5**)[18] and 2,2,4-trimethylpentane.[15] The increase in the reaction rate after the break was attributed to a free-radical-induced decomposition of DMD.[15] This process is initiated

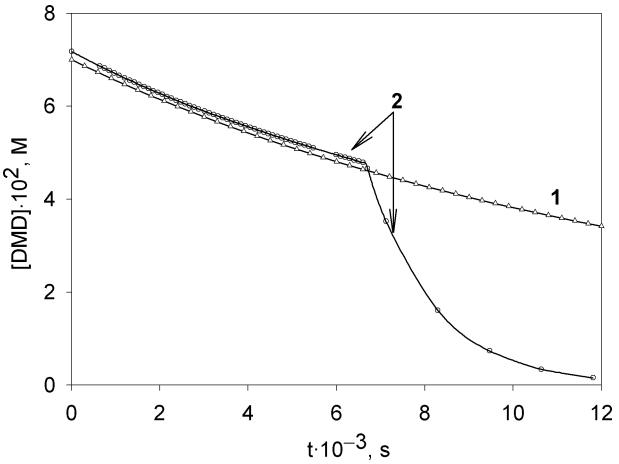


Fig. 1 The typical kinetic curves of DMD consumption in oxidation of **1** in CCl_4 at 30 °C (1: solution saturated with oxygen during the whole period of oxidation, 2: solution saturated with oxygen only before starting the experiment $[O_2]_0 = 5 \times 10^{-3}$ M).

by a decrease in the concentration of the oxygen in solution, so that alkyl radicals, formed in this reaction, can not be trapped by O_2. At the same time reaction in a solvent saturated with oxygen allows the rapid transformation of the alkyl radicals into peroxyl radicals, which are consumed by recombination according to the Russell mechanism giving molecular products.[23] Under these conditions DMD is not consumed in a competitive reaction, and the yield of products increases (Table 1).

In oxygenated solutions the kinetics of oxidation of **1–4** by DMD follow a second order reaction, but first order for both dimethyldioxirane and the substrate (RH), respectively:

$$-\mathrm{d[DMD]}/\mathrm{d}t = k[\mathrm{RH}][\mathrm{DMD}].$$

The pseudo-first order reaction is observed in the presence of excess substrate:

$$k_{\mathrm{eff}} = k[\mathrm{RH}]_0, \text{ if } [\mathrm{RH}]_0 >> [\mathrm{DMD}]_0,$$

therefore, the effective rate constant can be derived from the equation:

$$-\mathrm{d[DMD]}/\mathrm{d}t = k_{\mathrm{eff}}[\mathrm{DMD}]$$

The linear dependence of the effective rate constants on the initial concentration of the substrate $[RH]_0$ indicates a first order reaction with respect to the substrate RH. Also, good agreement was found between the bimolecular rate constants, calculated from the dependence of k_{eff} upon $[RH]_0$ and measurements using equimolar ratios of reagents.

For hydrocarbon **3** the yield of alcohol is independent of molecular oxygen content in the reaction solution (Table 1). The same results were found for oxidation of binor-S by DMD, on the basis of which it was concluded that dioxiranes react with a substrate *via* O-insertion into the C–H bond.[11] Thus, in the case of some hydrocarbons, such as **3** and binor-S, oxidation occurs either without the escape of radicals from a solvent cage, or the contribution of the radical channel is insignificant.

The Arrhenius parameters for oxidation of the cage hydrocarbons **1–4** by DMD are summarized in Table 2 (over a temperature range of +18° to +70 °C). Experimentally determined activation energies range from 12.1 to 19.6 kcal mol^{-1}. The negative values of the entropy of activation indicate highly-ordered transition states.

The data obtained can be explained by the mechanism presented in Scheme 3, which combines two parallel channels. The concept has been expressed in the literature as the concerted and molecule-induced homolytic/rebound mechanism.[3,12–15,18] The relatively low values of the entropies of activation obtained here for the oxidation of cage hydrocarbons are unexpected for general reactions of radical abstraction ($R–H + {}^{\bullet}OR_3$), such as, for example, hydrogen abstraction by oxygen-centred radicals.[24] At the same time the good yields of alcohols (Table 1) and the high selectivity of oxidation, even in the presence of the radical channel, indicates the predominance of the cross-reaction between the peroxy radicals of cage hydrocarbons ($ROO^{\bullet}$) and $MeOO^{\bullet}$, formed from the dioxirane, which would react in accordance with the Russell mechanism as shown in Scheme 3.

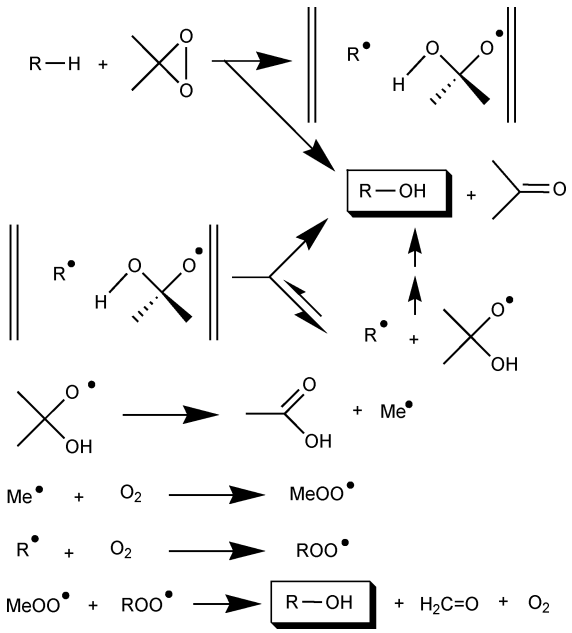
If a degenerate branching chain reaction of peroxy radicals with a hydrocarbon ($ROO^{\bullet} + RH \rightarrow ROOH + R^{\bullet}$) were to provide an appreciable contribution to the process, then numerous products of oxidation would have been observed, and the yield of alcohols would depend upon the initial concentration of the substrate $[RH]_0$, but this was not found even with a 10-fold excess of the substrate. Also, if *homo*-recombination of peroxy radicals dominated over *cross*-recombination, the yield of alcohol would be lower than observed in our experiments. This hypothesis is supported by analysis of the rate constants of peroxy radicals in recombination reactions. The rate constant of the recombination of methylperoxy radicals is higher than that of $ROO^{\bullet}$ by several orders of magnitude ($k_{\mathrm{MeOO}} = 3.9 \times 10^8$ L mol^{-1} s^{-1} at 295 K;[25] $k_{\mathrm{ROO}} < k_{t\text{-BuOO}} = (1.6–15) \times 10^3$ L mol^{-1} s^{-1} at 295 K[26]). Consequently, the steady-state concentration of $ROO^{\bullet}$ can be determined from the equations:

$$[\mathrm{ROO}^{\bullet}] = [\mathrm{MeOO}^{\bullet}](k_{\mathrm{MeOO}}/k_{\mathrm{ROO}})^{1/2}, \therefore [\mathrm{ROO}^{\bullet}] < 161[\mathrm{MeOO}^{\bullet}]$$

Table 2 Kinetic parameters for oxidation of **1–4**, adamantane and acetone by DMD (in CCl_4, 18–70 °C)

Compound	$k(30\ ^\circ\mathrm{C}) \times 10^4$/ L mol^{-1} s^{-1}	E_a/kcal mol^{-1}	lg A/L mol^{-1} s^{-1}	R^2	$\Delta H^{\neq}_{298}$/kcal mol^{-1}	$\Delta S^{\neq}_{298}$/cal K^{-1} mol^{-1}	$\Delta G^{\neq}_{298}$/kcal mol^{-1}
1	2.34 ± 0.01	17.4 ± 0.3	8.9 ± 0.1	0.9992	16.8	−19.8	22.7
2	2.87 ± 0.01	14.9 ± 0.4	7.2 ± 0.1	0.9984	14.3	−27.5	22.5
3	43.7 ± 0.1	12.1 ± 0.1	6.42 ± 0.08	0.9995	11.5	−31.1	20.8
4	2.25 ± 0.01	19.6 ± 0.5	10.5 ± 0.2	0.9990	19.0	−12.5	22.7
Adamantane [a]	17.8 ± 0.1	14.0 ± 0.2	7.33 ± 0.09	—	13.4	−26.9	21.4
Acetone[b]	0.0020 ± 0.0002	23.2 ± 0.3	8.7 ± 0.2	—	22.6	−20.7	28.8

[a] Reference 18, the oxidation of adamantane by DMD in CCl_4. [b] Reference 15.



Scheme 3

Unfortunately, there are very few results on the reaction rate constants of the *cross*-recombination of primary peroxy radicals with tertiary peroxy radicals. But analysis of available experimental data demonstrates that the rate constant of this type of recombination is one order of magnitude lower than that of the *homo*-recombination of primary peroxy radicals. In our case, the cross-reaction ($MeOO^{\bullet}$ + $ROO^{\bullet}$) will dominate with a rate constant $k \geq 10^6$ L mol^{-1} s^{-1}, and this value is in agreement with the literature data on the rate constants for this type of reaction.[18,24,27]

The low yield of alcohol **2a** can be explained by the fact that the tricyclo[3.2.2.0^{2,4}]nonan-1-yl formed and/or the product of its reaction with oxygen can undergo isomerization with the opening of the cyclopropylic fragment at the β-position with respect to the reaction centre.

Oxidation of **1–4** by TFD occurs much faster than by DMD. Reaction times vary from one minute for hydrocarbon **3** to twenty for compound **4**. Apparently, the oxidation by TFD is characterized by the absence of free radical processes.

This experimental study of the reaction of cage hydrocarbons with DMD was carried out in parallel with a theoretical study of the oxidation reactions employing DFT calculations. The molecular geometries of reactants, products and transition states, as well as the corresponding energies of the activation barriers for oxidation of cage hydrocarbons **1–4** and adamantane (**5**) by DMD were calculated at the B3LYP/6-31G(d) level and further improved with B3LYP/6-311 + G(d,p) calculations in a single-point fashion. The transition state (TS) structures of the reaction of dimethyldioxirane with cage hydrocarbons are shown in the supporting information.† The energy parameters of TS formation are summarized in Table 3. As can be seen from a comparison of experimental and calculated activation free energies, the correlation is poor (Fig. 2). The reasons for this exception are not clearly understood and require further clarification. Even inclusion of the solvent effect with the COSMO model and the CCl_4 dielectric constant of 2.228 in the single-point fashion does not significantly improve the results. The differences in Gibbs free energy is approximately ±1 kcal mol^{-1} as can be seen in Table 3. This could be due to errors in the calculation of the energies of polycyclic systems.[28] Unfortunately, recalculation of energies using B3PW91/6-311 + G(d,p)//B3LYP/6-31G(d), and also calculation at the B3PW91/6-31 + G(d) level of theory

Table 3 Theoretical activation parameters from computation using restricted wave functions for oxidation of **1–4** cage hydrocarbons (from TS1-C to TS4-C respectively), adamantane (TS5-C) and acetone (TS6-C) by dimethyldioxirane computed at various levels of theory

Transition structure	Method	ΔE_a/kcal mol^{-1}	$\Delta S^{\neq}_{298}$/cal K^{-1} mol^{-1}	$\Delta H^{\neq}_{298}$/kcal mol^{-1}	$\Delta G^{\neq}_{298}$/kcal mol^{-1}	$\Delta G^{\neq}_{CCl4}$/kcal mol^{-1}
TS1-C	B3LYP/6-31G(d)	25.4	−35.6	24.8	35.5	35.1
	B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d)	18.4	—	17.8	—	—
	B3PW91/6-311 + G(d,p)//B3LYP/6-31G(d)	20.5	—	20.9	31.5	—
	B3PW91/6-31 + G(d)	24.7	−34.5	25.1	35.4	—
TS2-C	B3LYP/6-31G(d)	29.1	−34.1	28.5	38.6	37.7
	B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d)	21.7	—	21.1	—	—
	B3PW91/6-311 + G(d,p)//B3LYP/6-31G(d)	23.7	—	24.1	34.3	—
	B3PW91/6-31 + G(d)	27.9	−33.3	28.4	38.3	—
TS3-C	B3LYP/6-31G(d)	22.4	−35.0	21.9	32.3	32.0
	B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d)	15.0	—	14.5	—	—
	B3PW91/6-311 + G(d,p)//B3LYP/6-31G(d)	17.1	—	17.6	28.0	—
	B3PW91/6-31 + G(d)	21.3	−35.9	21.7	32.4	—
TS4-C	B3LYP/6-31G(d)	26.8	−34.0	26.4	36.5	37.2
	B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d)	19.7	—	19.3	—	—
	B3PW91/6-311 + G(d,p)//B3LYP/6-31G(d)	21.9	—	22.6	32.7	—
	B3PW91/6-31 + G(d)	26.2	−34.9	26.7	37.1	—
TS5-C	B3LYP/6-31G(d)	28.1	−29.5	27.5	36.3	35.5
	B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d)	20.3	—	19.7	—	—
	B3PW91/6-311 + G(d,p)//B3LYP/6-31G(d)	22.2	—	22.7	31.5	—
	B3PW91/6-31 + G(d)	26.4	−29.7	27.0	35.8	—
TS6-C	B3LYP/6-31G(d)	39.3[a]	−29.6[a]	38.0[a]	46.3[a]	48.5[b]
	B3PW91/6-31 + G(d)	39.1	−32.9	39.1	49.1	—

[a] Reference 17. [b] CH_2Cl_2, reference 17.

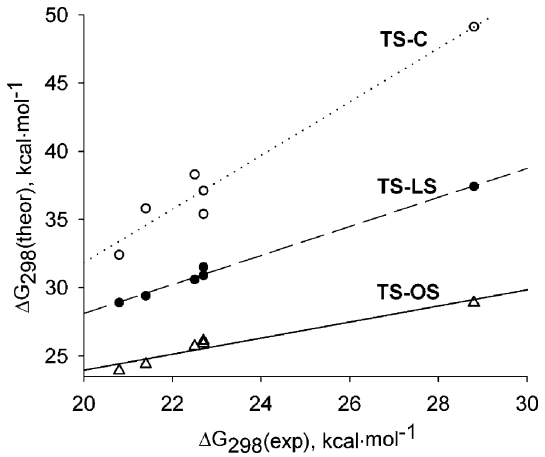


Fig. 2 Correlation between experimental $\Delta G^{\neq}_{298}$ and theoretical data, calculated at the (U)B3PW91/6-31 + G(d) level, for oxidation of cage hydrocarbons by DMD.

does not lead to any substantial improvement in the correlation between experimental and theoretical results.

However, in the case of reactions possibly involving radical (biradical) intermediates, the problem arises in the choice of an adequate method for quantum chemical calculations. The standard calculation schemes based on the use of restricted wave functions for closed shells (restricted Hartree–Fock or Kohn–Sham methods) are inappropriate in such situations. It has previously[17] been shown that the wave functions calculated[29] for the transition state of the reactions of dioxiranes with alkanes, aldehydes, and alcohols have singlet–triplet instability, *i.e.*, there is another unrestricted solution of the Schrödinger (or Kohn–Sham) equation with nonequivalent α and β orbital manifolds, which is lower in energy. Calculation methods that take into account the multiconfigurational character of the wave function are necessary for the adequate description of systems of biradical nature. However, such calculations are computationally intensive and time-consuming. The DFT calculations of (bi)radicals using the hybrid functional as in B3LYP in the unrestricted variant (UB3LYP) with broken α–β symmetry were shown[30] to give results, whose quality are comparable with the state-of-the-art multi-reference coupled cluster calculations (MR-AQCC). In this work, we used the UB3PW91 method to calculate the reactions of DMD with alkanes. The B3PW91 was chosen because it allows one to calculate in a correct manner the energy of polycyclic systems.[28] Generally, in calculations of singlet biradicals within the framework of the unrestricted hybrid DFT methods, such as UB3LYP and UB3PW91, fairly strong spin contamination is inevitable: the $\langle S^2 \rangle$ value can be considerably higher than zero, which indicates a significant radical character of the molecular wave function. It is known[31] that the thermochemical and geometric parameters calculated by the hybrid DFT methods are less prone to the influence of spin contamination than those obtained by the HF, MP2, CC, and other methods.

As a test, possible reaction pathways for the 2-methylpropane–DMD system using B3PW91 were calculated. Results (Fig. S2, ESI†) are in good agreement with literature data for this system at the B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d), B3LYP/6-311 + G(d,p) and CCSD(T)/cc-VTZ2P + f,d levels of theory.[3,12,17]

Also in agreement with the above and previous work,[12,17] the transition states can be described as two structures: TS-LS, the molecule-induced homolytic pathway, and TS-OS—the radical reaction with OS-$^1A_1$-DMD. The radical reaction with OS-$^3A_1$-DMD *via* TS–T is possible, but improbable, therefore we shall not consider it further. The two structures TS-LS and TS-OS (Fig. 3) can be considered as extreme variants of a transitive condition for this system.

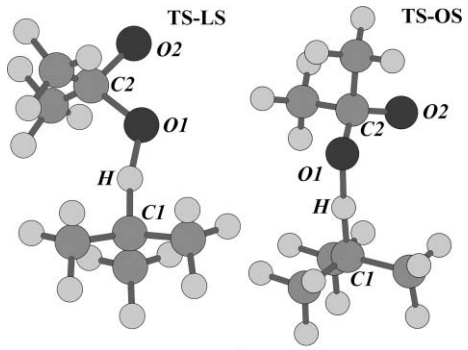


Fig. 3 Geometry of transition structures TS-LS and TS-OS for oxidation of 2-methylpropane with DMD at the UB3PW91/6-31 + G(d) level.

As shown earlier[17] TS-LS can lead to molecular products and due to the fact that intermediates in this process are radical pairs, some of the radicals probably escape from the cage thus leading to radical chain processes.

The results obtained for TS-LS and TS-OS transition states agreed better with values obtained experimentally (Table 4, Fig. 2). The kinetic isotope effect previously measured[14] for oxidation of methylcyclohexane by DMD is also better described by the transition states having a radical character (Table 5). Thus, the TS of oxidation of the C–H bond by DMD have a radical character.

In some cases the reaction of DMD with hydrocarbons leads to the formation of radicals but in others the oxidation occurs without radicals being observed. What is the mechanism of interaction of cage hydrocarbons with DMD? Comparison of experimental with theoretical results showed that the TS have a radical character as proposed in previous theoretical work.[3,12,17] The further evolution of the process leads to the formation of a singlet radical pair complex,[17] which can rapidly decompose and/or transform, depending upon the nature of the interacting radicals. Thus, changing the electron-donating group on the substrate to an electron-withdrawing group leads to an increase in the contribution of the radical channel, as shown for the oxidation of a series of *p*-substituted analogues of 1-methoxy-1-phenylethane by DMD.[32] Along with the nature of the substrate, the solvent itself, apparently, can destabilize the radical pair complex, leading to the formation of free radicals. It has been reported[14] that the oxidation of cyclohexane in the gas phase proceeds almost completely by the no-free-radical mechanism, whereas the reaction in a solution of acetone[15] occurs with significant contribution of the radical processes. Previously, we have reported a detailed study of adamantane oxidation by DMD.[18] It was shown that the reaction of interest has two possible channels: first, the absence of the formation of free radicals; and second, with the escape of radicals from a solvent cage. The contribution of the radical channel in the oxidation of adamantane increases continuously with increasing

Table 4 Theoretical activation energies and selected geometrical parameters from computations using unrestricted variants of wave functions for oxidation of **1–4** (TS1-LS and TS1-OS to TS4-LS and TS4-OS respectively), adamantane (TS5-LS, TS5-OS), and acetone (TS6-LS, TS6-OS) by DMD at the B3PW91/6-31 + G(d) level

Transition structure	$\langle S^2 \rangle$	C^1–H/Å	H–O^1/Å	O^1–O^2/Å	$\angle C^1HO^1$/°	$\angle O^1C^2O^2$/°	ΔE_a/kcal mol^{-1}	$\Delta S^{\neq}_{298}$/cal K^{-1} mol^{-1}	$\Delta H^{\neq}_{298}$/kcal mol^{-1}	$\Delta G^{\neq}_{298}$/kcal mol^{-1}
TS1-LS	0.43	1.266	1.258	1.920	171.0	86.9	20.1	−35.4	20.4	30.9
TS2-LS	0.50	1.278	1.232	1.957	169.0	88.9	20.4	−33.2	20.7	30.6
TS3-LS	0.39	1.254	1.278	1.911	167.2	86.4	17.9	−35.7	18.2	28.9
TS4-LS	0.46	1.273	1.252	1.938	169.3	87.8	20.5	−35.9	20.8	31.5
TS5-LS	0.47	1.269	1.244	1.943	168.1	88.2	19.9	−30.9	20.2	29.4
TS6-LS	0.68	1.316	1.188	1.982	170.5	89.7	27.5	−32.8	27.6	37.4
TS1-OS	0.94	1.221	1.383	2.323	172.9	116.4	15.2	−35.2	15.5	26.1
TS2-OS	0.93	1.229	1.355	2.319	171.7	116.1	15.2	−33.6	15.6	25.7
TS3-OS	0.93	1.207	1.418	2.321	170.6	116.4	13.1	−34.8	13.5	23.9
TS4-OS	0.91	1.239	1.352	2.325	168.2	116.6	15.1	−38.4	15.5	25.9
TS5-OS	0.93	1.222	1.370	2.320	170.0	116.2	14.6	−31.0	15.1	24.4
TS6-OS	0.94	1.269	1.270	2.317	176.4	115.7	19.0	−32.9	19.1	28.9

Table 5 Selected geometrical parameters and kinetic isotopic effect for oxidation of methylcyclohexanes H_{14} and D_{14}, the fully hydrogenated and deuterated compounds, by DMD (TS7) at the B3PW91/6-311 + G(d,p) level

Transition structure	$\langle S^2 \rangle$	C^1–H/Å	H–O^1/Å	O^1–O^2/Å	$\angle C^1HO^1$/°	$\angle O^1C^2O^2$/°	$\angle HO^1O^2$/°	μ/D	$-\delta\Delta G^{\neq}$/cal mol^{-1}	k_H/k_D, at 0 °C
TS7-C	0.000	1.452	1.065	2.044	155.5	93.1	155.7	7.73	758.7	4.05
TS7-LS	0.358	1.251	1.270	1.890	171.0	85.3	163.7	4.56	945.7	5.72
TS7-OS	0.929	1.200	1.427	2.314	172.1	116.5	93.7	1.75	804.5	4.41
Experiment	—	—	—	—	—	—	—	—	—	6.05 ± 0.27[a]

[a] Reference 14.

temperature, in a fashion similar to the formation of radicals, which originate from the solvent cage upon the decomposition of normal radical initiators such as azabisisobutyronitrile (AIBN).[33] These facts can only be explained if both the radical pathway and the other pathway (without free radicals) have very similar Arrhenius parameters. Both pathways probably have a common TS and the free radicals form after the TS.[18]

In oxidation reactions with participation of TFD, the presence of free radicals was not observed here as previously reported in the literature.[5–7,10] The reason for this phenomenon could be attributed to the insufficient electron density on the carbon atom due to the presence of the strong electron-withdrawing group – CF_3, which contributes to the stabilization of a singlet radical pair complex (leading to increases in the stability constant). It probably also facilitates the isomerization of the radical pair through the reduction of the activation barrier of migration of the hydroxyl group to the substrate radical leading to the formation of either the corresponding alcohol or ketone.

The fact that the oxidation of the chiral substrates occurs with the conservation of chirality[34] and that the oxyfunctionalization of compounds with a cyclopropyl fragment occurs without the destruction of the fragment,[7–9,19] have been used as decisive arguments for the concerted insertion of an oxygen atom into the C–H bond.[19] However, spin density on the carbon atom of the substrate in the TS is not so high (0.65 ÷ 0.25) and we suggest that it is not enough for isomerization of hypersensitive radical clocks with a rearrangement time comparable with the lifetime of the TS. After the TS, radicals in a singlet radical pair complex do not possess properties characteristic of free radicals and also the isomerization of clock radicals in such complex should have much lower rate constants. Moreover, the last step, the "oxygen rebound" S_H2 process, for this diradical pair has a very low activation barrier of about 0.5 kcal mol^{-1}.[17] The complex must also have a rigid structure which fixes the configuration not allowing the radicals to rotate in this stage of the reaction. This leads to very little change in chirality, low isomerization of clock radicals and high product selectivity.[4–6]

Conclusions

We have shown experimentally and theoretically that oxidation of cage hydrocarbons by DMD can occur through radical transition states, which can generate free radicals, but it may also occur without producing radical products. The reaction with TFD is characterized by much faster reaction rates and by the absence of free radicals. The role of radicals can be very important in oxidation by dioxiranes and it depends upon the structure of the substrate and of the dioxirane itself.

Experimental

Materials and methods

The GC analyses were run using a capillary column (30 m × 0.25 μm id, OV-101) on a "Shimadzu" chromatograph, 1,1,1,2-tetrachloro-2,2-difluoroethane was used as an internal standard. Column chromatography was performed on silica gel (230–400 mesh), continuously increasing the concentration (up to a 2 : 1 ratio) of Et_2O in *n*-hexane. The MS analyses were performed in EI mode (70 eV) on a high-resolution mass spectrometer Thermo Finnigan MaT95XP and/or GC-MS Hewlett Packard HP5980 (capillary column HP5; 60 m × 0.25 mm) with

mass-detector HP5972A. The ^{1}H NMR spectra were recorded on a 500 MHz "Varian" NMR-spectrometer and/or 300 MHz "Bruker" spectrometer, resonances were referenced to a residual isotopic impurity: $CHCl_3$ (7.26 ppm) in $CDCl_3$, used as solvent. The ^{13}C NMR spectra (125.759 MHz and/or 75 MHz) were referenced to the middle peak of the $CDCl_3$ solvent (77.00 ppm). IR spectra were obtained in KBr or NaCl on a Specord M80 Carl Zeiss Jena.

1,1,1-Trifluoro-2-propanone (TFP) (bp 22 °C), purchased from Aldrich, was purified by fractional distillation over granular P_2O_5, and redistilled prior to use. Acetone of HPLC grade was stored over 4 Å molecular sieves, and routinely distilled on the rectification column. Commercial starting materials, CCl_4, and other solvents were purified by standard methods. Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) from Aldrich was used in the synthesis of dioxirane. The solution of 0.9–1.1 M of methyl(trifluoromethyl)dioxirane (TFD) in TFP[35] and the solution of 0.08–1.4 M of dimethyldioxirane (DMD) in acetone[36] were synthesized according to the standard procedures. The extraction of DMD from acetone into CCl_4 was done by the routine technique.[37]

Spiro{cyclopropan-1′,7-2-methylbicyclo[2.2.1]heptan-(*Z*)-2-ol} (1a)

Oxidation by DMD: **1** (136 mg, 1.0 mmol), dissolved in CCl_4 (1 mL), was mixed at 20 °C with 0.5 eq. of DMD (4.2 mL, 0.12 M, CCl_4, 0.5 mmol), the solution was saturated with oxygen, and the reaction was monitored by GC. After 7 days, the solvent was removed by vacuum and the residue was separated by column chromatography on SiO_2 and afforded **1a** (66 mg, 0.43 mmol, yield 87%) as a colourless oil and a starting material (67 mg, 0.49 mmol).

Oxidation by TFD: **1** (136 mg, 1.0 mmol) was dissolved in CCl_4 (1 mL) and mixed at 0 °C with 1 eq. of dioxirane (1.7 mL, 0.6 M, TFP, 1.0 mmol). The reaction was monitored by GC. After 15 min the solvent was removed by vacuum, and column chromatography gave pure (99%+, by GC) **1a** (149 mg, isolated yield, 98%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 2.20 (br. s, 1H, OH), 1.84 (ddd, $J = 13.1$ Hz, $J = 4.8$ Hz, $J = 2.6$ Hz, 1H, 3-H_{exo}), 1.77–1.58 (m, 2H, 5-H_{exo} and 6-H_{exo}), 1.53–1.41 (m, 3H, 4-H, 6-H_{endo}, 1-H), 1.37–1.32 (m, 1H, 3-H_{endo}), 1.28 (s, 3H, CH_3), 1.19–1.11 (m, 1H, 5-H_{endo}), 0.81–0.74 and 0.71–0.63 (m, 2H, 2′-H), 0.40–0.28 (m, 2H, 3′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.06 (C-3′), 6.50 (C-2′), 23.85 (C-6), 24.61 (CH_3), 27.68 (C-5), 34.57 (C-7), 42.77 (C-4), 49.99 (C-3), 53.14 (C-1), 79.48 (C-2). GC-MS (70 eV) *m*/*z* (rel. intensity): 152 (M^+, 7.3), 137 ($M^+ - CH_3$, 7.0), 134 ($M^+ - H_2O$, 8.3), 123 ($M^+ -$ CHO, 9.3), 119 ($M^+ - H_2O - CH_3$, 14.2), 109 ($M^+ - C_2H_3O$, 30.9), 94 ($M^+ - CH_2C(O)CH_3$, 80.4), 79 ($M^+ - C_6H_7$, 100), 67 (27.0), 43 (79.6). IR (NaCl) *v* 3432 (OH), 3072, 2952, 2872, 1740, 1444, 1424, 1380, 1344, 1312, 1268, 1220, 1192, 1176, 1152, 1124, 1100, 1072, 1008, 952, 939, 916, 880, 844, 800 cm^{-1}. Anal. calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59; found: C, 77.20; H, 10.70%.

Tricyclo[3.2.2.0^{2,4}]nonan-1-ol (2a)

Oxidation by DMD: **2** (122 mg, 1.0 mmol), dissolved in CCl_4 (1 mL), was mixed at 20 °C with 0.5 eq. of DMD (4.6 mL, 0.11 M, CCl_4, 0.5 mmol), and the reaction was monitored by GC. After 7 days, the solvent was removed by vacuum and the residue was separated by column chromatography on SiO_2 giving **2a** (47 mg, 0.34 mmol, yield 68%) as a white solid and the starting material (60 mg, 0.49 mmol).

Oxidation by TFD: **2** (122 mg, 1.0 mmol) was dissolved in CCl_4 (1 mL) and mixed at 0 °C with 1 eq. of dioxirane (1.7 mL, 0.6 M, TFP, 1 mmol). The reaction was monitored by GC. After 15 min the solvent was removed by vacuum, and column chromatography yielded pure (99%+, by GC) **2a** (135 mg, isolated yield, 98%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 2.36 (br. s, 1H, OH), 1.88–1.60 (m, 4H), 1.58–1.45 (m, 1H, 5-H), 1.42–1.30 (m, 4H), 1.18–1.02 (m, 1H, 2-H), 1.00–0.88 (m, 1H, 4-H), 0.65–0.56 (m, 1H, 3-H), 0.40–0.30 (m, 1H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.02 (C-3), 15.88 (C-4), 19.26 (C-2), 23.42 (C-6), 24.41 (C-5), 29.93 (C-8), 32.75 (C-7), 34.04 (C-9), 70.64 (C-1). GC–MS (70 eV) *m*/*z* (rel. intensity) 138 (M^+, 36), 131 (25), 123 (23), 119 (26), 110 (24), 109 (100), 105 (16), 97 (17), 96 (34), 95 (89), 94 (21), 93 (26), 92 (20), 91 (44), 83 (40), 82 (19), 81 (35), 80 (21), 79 (79), 77 (32), 70 (24), 69 (72), 67 (42), 65 (16). HRMS calcd for $C_9H_{14}O$ 138.1045, found 138.1044. IR (KBr) *v* 3268 (OH), 1732, 1462, 1378, 1348, 1294, 1108, 1030, 1018, 946, 922, 904, 814, 724 cm^{-1}.

***exo-endo-endo*-Heptacyclo[9.3.1.0^{2,10}.0^{3,8}.0^{4,6}.0^{5,9}.0^{12,14}]pentadecan-2-ol (3a)**

Oxidation by DMD: **3** (198 mg, 1.0 mmol), dissolved in CCl_4 (2 mL), was mixed at 20 °C with 0.5 eq. of DMD (4.6 mL, 0.11 M, CCl_4, 0.5 mmol), and the reaction was monitored by GC. After 1 day, the solvent was removed by vacuum, and the residue was separated by column chromatography on SiO_2 and gave **3a** (103 mg, 0.49 mmol, yield 98%) as a white solid and the starting material (99 mg, 0.47 mmol, yield 94%).

Oxidation by TFD: **3** (198 mg, 1.0 mmol), dissolved in CCl_4 (2 mL), was mixed at 0 °C with 1 eq. of dioxirane (1.7 mL, 0.6 M, TFP, 1 mmol). The reaction was monitored by GC. After 5 min the solvent was removed by vacuum, and column chromatography yielded pure (99%+, by GC) **3a** (210 mg, isolated yield, 98%) as a white solid.

Mp 77.5–78.5 °C. ^{1}H (500 MHz, $CDCl_3$) δ 0.09 and 0.66 (both dt, $^2J_{syn,anti} = 5.4$ Hz, $J_{13,14/12;cis} = 7.0$ Hz, $J_{13,14/12;trans} = 3.0$ Hz, 2H, 13-H), 1.10 (br. dt, $J_{5,9} = 2.1$ Hz, $J = 5.5$ Hz, 1H, 5-H), 1.14 (br. dt, $J_{4,3} = 2.1$ Hz, $J_{4,5} = 5.5$ Hz, $J_{4,6} = 5.5$ Hz, 1H, 4-H), 1.18 (m, 1H, 14-H), 1.19 (m, 1H, 6-H), 1.22 (m, 1H, 12-H), 1.26 and 1.30 (both dt, $^2J_{gem} = 10.8$ Hz, $J = 1.5$ Hz, 2H, 7-H), 1.20 (m, 1H, 15-H_{anti}), 1.36 (dq, $^2J_{gem} = 10.9$ Hz, $J = 1.2$ Hz, 1H, 15-H_{syn}), 1.67 (br. s, 1H, OH), 1.99 (br. t, $J = 2.1$ Hz, 1H, 3-H), 2.02 (br. t, $J \approx 4.0$ Hz, 1H, 10-H), 2.08 (dt, $J_{9,10} \approx 4.0$ Hz, $J \approx 2.1$ Hz, 1H, 9-H), 2.27 (dt, $J_{1,11} = 1.5$ Hz, $J_{1,15} = 1.2$ Hz, 1H, 1-H), 2.39 (m, $J_{10,11} \approx 3.8$ Hz, $J \approx 1.2$–1.5 Hz, 1H, 11-H), 2.44 (m, 1H, 8-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.39 (C-13), 13.66 (C-14), 13.67 (C-5), 13.84 (C-12), 14.07 (C-4), 16.64 (C-6), 27.34 (C-7), 29.98 (C-15), 39.46 (C-11), 45.45 (C-9), 47.34 (C-1), 48.06 (C-8), 53.32 (C-3), 61.44 (C-10), 89.04 (C-2). HRMS calcd for $C_{15}H_{18}O$ 214.136, found 214.135. GC-MS (70 eV) *m*/*z* (rel. intensity): 214 (M^+, 6.8), 199 ($M^+ -$ Me, 2), 196 ($M^+ - H_2O$, 5.5), 160 (3), 155 (4), 147 (5), 134 ($M^+ - C_6H_8$, 100), 129 (7), 119 (11), 116 (53), 105 (12), 91 (22), 81 (11), 79 (13), 77 (11), 69 (9), 65 (4), 55 (3). IR (KBr) *v* 3344 (OH), 1496, 1464, 1376, 1352, 1304, 1264, 1248, 1224, 1208, 1168, 1124, 1096, 1040, 1008, 984, 968, 920, 872, 836, 816, 784, 752, 728, 600, 520 cm^{-1}.

Anal. calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47; found: C, 84.5; H, 8.65%.

exo-exo-exo-Heptacyclo[9.3.1.$0^{2,10}$.$0^{3,8}$.$0^{4,6}$.$0^{5,9}$.$0^{12,14}$]pentadecan-2-ol (4a)

Oxidation by DMD: **4** (198 mg, 1.0 mmol), dissolved in CCl_4 (2 mL), was mixed at 20 °C with 0.5 eq. of DMD (4.6 mL, 0.11 M, CCl_4, 0.5 mmol), and the reaction was monitored by GC. After 1 day, the solvent was removed by vacuum and the residue was separated by column chromatography on SiO_2 giving **4a** (99 mg, 0.34 mmol, yield 93%) as a white solid and the starting material (98 mg, 0.49 mmol).

Oxidation by TFD: **4** (198 mg, 1.0 mmol) was dissolved in CCl_4 (2 mL) and mixed at 0 °C with 1 eq. of dioxirane (1.7 mL, 0.6 M, TFP, 1 mmol). The reaction was monitored by GC. After 15 min the solvent was removed by vacuum, and column chromatography yielded pure (99%+, by GC) **4a** (211 mg, isolated yield, 98%) as a white solid. Mp 78–79.5 °C. ^{1}H (500 MHz, $CDCl_3$) δ 0.23 (dt, $J_{syn,anti} = 5.8$ Hz, $J_{13,14/12;cis} = 7.0$ Hz, 1H, 13-H$_{anti}$), 0.71 (ddd, $J_{gem} = 11.8$ Hz, $J = 2.2$ Hz, $J = 1.7$ Hz, 1H, 15-H), 0.79 (dt, $J_{syn,anti} = 5.8$ Hz, $J_{13,14/12;trans} = 3.3$ Hz, 1H, 13-H$_{syn}$), 0.81 (t, $J = 4.3$ Hz, 1H, 12-H), 0.82 (t, $J = 5.3$ Hz, 1H, 5-H), 0.90 (dt, $J_{4,3} = 2.0$ Hz, $J_{4,5} = 5.1$ Hz, 1H, 4-H), 1.26 (m, 1H, 14-H), 1.36 and 1.35 (both t, $J = 1.5$ Hz, 2H, 7-H), 1.45 (tq, $J = 4.8$ Hz, $J = 1.2$ Hz, 1H, 6-H), 1.54 (dd, $J = 4.6$ Hz, $J = 2.4$ Hz, 1H, 10-H), 1.87 (br. s, 1H, OH), 1.98 (t, $J = 2.2$ Hz, 1H, 3-H), 2.06 (dt, $J = 4.6$ Hz, $J = 2.2$ Hz, 1H, 9-H), 2.13 (m, 1H, 15-H), 2.16 (dq, $J = 11.8$ Hz, $J = 1.4$ Hz, 1H, 11-H), 2.24 (m, 2H, 8-H and 1-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.68 (C-13), 11.84 (C-14), 12.96 (C-5), 14.29 (C-4), 16.77 (C-12), 20.04 (C-6), 22.76 (C-15), 27.94 (C-7), 37.89 (C-11), 41.64 (C-1), 42.94 (C-8), 46.18 (C-9), 53.88 (C-3), 59.24 (C-10), 90.60 (C-2). HRMS calcd for $C_{15}H_{18}O$ 214.136, found 214.137. GC-MS (70 eV) *m/z* (rel. intensity): 214 (M^+, 9.8), 199 ($M^+ - Me$, 2), 196 ($M^+ - H_2O$, 1.8), 160 (3), 155 (3), 147 (5), 134 ($M^+ - C_6H_8$, 100), 129 (6), 119 (9), 116 (49), 105 (10), 91 (19), 81 (10), 79 (11), 77 (10), 69 (3), 65 (3), 55 (3). IR (KBr) ν 3346 (OH), 1462, 1378, 1288, 1258, 1234, 1156, 1114, 1036, 1006, 976, 814, 712 cm^{-1}.

Calculations

All geometry optimizations were carried out at the Becke's three-parameters functional level with the LYP and PW91 correlation functionals named as B3LYP and B3PW91 hybrid density functionals[38] with the 6-311 + G(d,p), 6-31 + G(d) and 6-31G(d) basis sets,[39] using the Gaussian 98 suite of programs.[40] All studied structures and TSs were optimized without constraints. Vibrational frequencies and zero-point vibrational energies (ΔZPVE) were obtained at the same levels of theory and were scaled by a factor of 0.9806 for the B3LYP/6-31G(d) method;[41] other calculations were carried out without any scaling factors. The total electronic energies (E) and zero-point corrected energies (E + ZPVE) of all species of interest are summarized in the supporting information.†

^{13}C NMR isotropic chemical shifts of compounds **1–5**, products **1a–5a** and tetramethylsilane (TMS) as reference were performed in redundant internal coordinates using Schlegel's gradient optimization algorithm (calculating the energy derivatives analytically).[42] Carbon isotropic shielding constants of cage hydrocarbons and their corresponding alcohols $\sigma(^{13}C)_{Comp}$ were computed in the single-point fashion using the MPW1PW91 method[43] with 6-311 + G(2d,p) basis set and the continuous set of gauge transformations (CSGT) methodology.[44] Chemical shifts, $\delta(^{13}C)$, were normalized to a standard TMS according to the equation: $\delta(^{13}C) = \sigma(^{13}C)_{TMS} - \sigma(^{13}C)_{Comp}$, where the isotropic shielding constant of carbon atoms in TMS, $\sigma(^{13}C)_{TMS} = 182.60$ ppm.

Kinetic isotopic effects were calculated at the B3PW91/6-311 + G(d,p) level of theory using the definition KIE = k_D/k_H = $\exp(-\delta\Delta G^{\neq}/RT)$, $\delta\Delta G^{\neq} = \Delta G_H^{\neq} - \Delta G_D^{\neq}$, with $\Delta G_H^{\neq}$ and $\Delta G_D^{\neq}$ the activation free energies of the protonated and the deuterated species, respectively.[45]

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