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Novel Pathways for Oxygen Insertion into Unactivated C−H Bonds by Dioxiranes. Transition Structures for Stepwise Routes via Radical Pairs and Comparison with the Concerted Pathway

Mauro Freccero,[†] Remo Gandolfi,[†] Mirko Sarzi-Amadè,*,[†] and Augusto Rastelli[‡]

Dipartimento di Chimica Organica, Università di Pavia, V.le Taramelli 10, 27100 Pavia, Italy, and Dipartimento di Chimica, Università di Modena, Via Campi 183, 41100 Modena, Italy
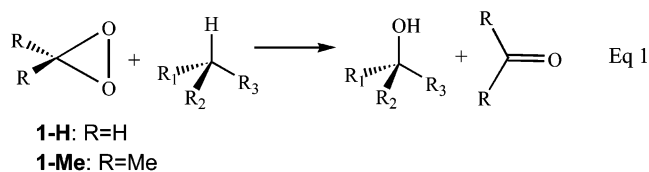
nmr@chifis.unipv.it

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The oxygen insertion into C−H bonds (of methane, isobutane, and acetone) by dioxiranes (parent dioxirane and dimethyldioxirane) to give alcohols was studied with the DFT theory, using both restricted and unrestricted B3LYP methods, and 6-31G(d) and 6-311+G(d,p) basis sets to evaluate the feasibility of stepwise mechanisms and their competition with the concerted counterpart. Confirming previous results by other authors, we have located, with the RB3LYP method, concerted TSs in which the oxygen bound to be inserted interacts very strongly with the hydrogen atom and very weakly with the carbon atom of the C−H bond. These TSs nicely explain all the experimental observations (e.g., configuration retention at the chiral centers), but all of them exhibit an RHF → UHF wave function instability that preclude considering them as genuine transition structures. We also were able to characterize, with UB3LYP methods, two alternative two-step processes that can lead to final products (alcohol + carbonyl compound) via singlet radical pair intermediates. For the first step of both processes we located genuine diradicaloid TSs, namely, TSs **rad,coll** and TSs **rad,perp**, that have stable wave functions. In TSs **rad,coll** the alkane C−H bond tends to be collinear with the breaking O_1- - -O_2 bond while in TSs **rad,perp** the alkane C−H bond is almost perpendicular to the O_1- - -O_2 bond. The first step, of both processes, can represent an example of a "molecule induced homolysis" reaction: collision between alkane and dioxirane brings about the homolytic cleavage of the dioxirane O−O bond and the hydrogen abstraction follows afterward to produce the diradicaloid TS that then falls down to a singlet radical pair. This hypothesis was fully confirmed by IRC analysis in the case of TSs **rad,coll**. The possible pathways that lead from the intermediate radical pair to final products are discussed as well as the hypothesis that the radical collinear TSs may collapse directly to products in a "one-step nonconcerted" process. However, diradical mechanisms cannot explain the experimental data as satisfactorily as the concerted pathway does. As for computational predictions about competition of diradical vs concerted mechanisms, they strongly depend (i) on the alkane C−H type, (ii) on whether gas phase or solution is considered, and (iii) on the basis set used for calculations. In short, the concerted TS benefits, with respect to the corresponding diradicaloid TSs, of alkyl substitution at the C−H center, solvation effects, and basis set extension. Actually, in the case of DMD reactions with methane and acetone, the diradicaloid TSs are always (both in gas phase and in solution and with both the basis sets used) strongly favored over their concerted counterpart. In the case of DMD reaction with isobutane tertiary C−H bond the large favor for the diradicaloid TSs over the concerted TS, predicted in gas phase by the B3LYP/6-31G(d) method, progressively decreases as a result of basis set extension and introduction of solvent effects: the higher theory level [B3LYP/6-311+G(d,p)] suggests that in acetone solution TS **conc** has almost the same energy as TS **rad,perp** while TS **rad,coll** resides only 2 kcal/mol higher.

Introduction

Dioxiranes exhibit a truly noteworthy and synthetically useful capacity to insert oxygen into unactivated alkane C−H bonds (eq 1) under mild conditions.[1]

1-H: R=H
1-Me: R=Me

The mechanism of this reaction has been the subject of a hot controversial debate focused on the concerted-stepwise dichotomy (Schemes 1 and 2). Curci, Adam, and others advanced a one-step oxygen insertion (a concerted

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SCHEME 1. Curci–Adam "Concerted" Mechanism
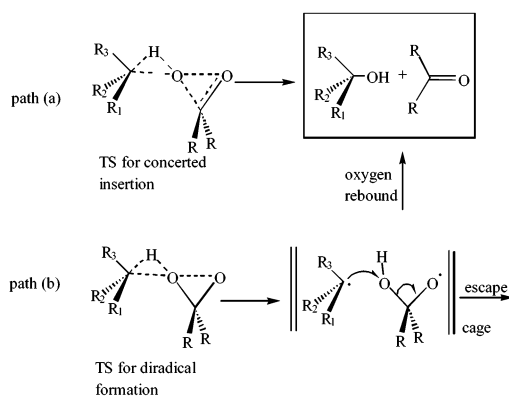
SCHEME 2. Minisci Stepwise Mechanism
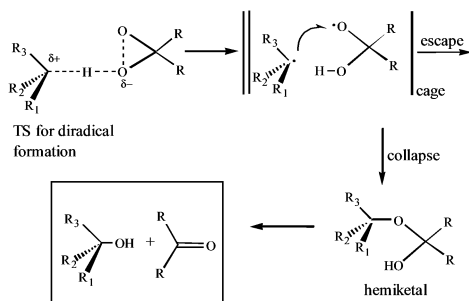
electrophilic process via a spiro TS, path (a) in Scheme 1)[2] while, in contrast, Minisci proposed a stepwise mechanism (a "molecule induced homolysis" process) via a radical pair (Scheme 2) that can either collapse to hemiketal or generate out-of-cage *free* radicals.[3] The most compelling evidence for the concerted mechanism comes from the complete configuration retention, observed for oxygen insertion at a chiral center,[2c] and from radical clock studies.[2c,4] Minisci's mechanism is supported by formation of radical derived products (such as alkyl bromides) in dioxirane hydroxylation carried out in the presence of CBrCl₃ and in the absence of oxygen.[3a]

Curci–Adam also argued that a concerted mechanism (path (a) in Scheme 1) is experimentally hard to distinguish from a stepwise process (path (b) in Scheme 1) in which the TS evolves into a caged radical pair that in turn undergoes a fast S_H2 reaction ("oxygen rebound mechanism") to directly form the final ketone + alcohol mixture.[2c]

From a theoretical standpoint, it is important to recall that only recently the electronic structure (ground and excited states) of dioxiranes **1** [dioxirane (DHD) **1-H**;

dimethyldioxirane (DMD) **1-Me**, Figure 1] as well as the mechanism of their ring opening to give the dioxymethane diradicals **2** (**2-H** and **2-Me**, respectively, Figure 1) has been satisfactorily described.[5a–7] In particular, it was shown that ground-state symmetric ring opening of dioxiranes **1**, with 4p π electrons,[8a] yields the dioxymethanes in their ground state, i.e., **2** with 2p π electrons and singlet diradical character.[8b]

Two optimized conformers of 2-hydroxyisopropoxy radical, the putative intermediate of radical reactions of DMD (Schemes 1 and 2), are also reported in Figure 1, with the synclinal isomer (**syn-3-Me**, <H−O−C−O = 20°) more stable than its anti (**anti-3-Me**, <H−O−C−O = 180°) counterpart by 3.2 kcal/mol.[9,10]

Three groups independently addressed the important mechanistic issue of the hydroxylation of alkanes by dioxiranes by locating concerted (**conc**) TSs [path (a) in Scheme 3].[11–13] In these TSs, the dioxirane O_1- - -O_2 bond is substantially broken and the O_1−H bond is almost completely formed, while the C_4- - -O_1 bond formation is still at the very beginning.[11–13]

According to IRC analysis carried out by Bach[11] and Houk,[12] these TSs are directly connected to reactants on one side and to products on the other side without any radical pair intermediate. On the other hand, Rauk suggested the presence of a bifurcation on the descent path to products: the reaction path divides (at a point located ≈ 2 kcal/mol below the TS) into two channels leading, respectively, to the alcohol and ketone (path (a_1)) or to the radical (2-hydroxyalkoxyl radical + alkyl radical) pair (path (a_2)) (Scheme 3).[13]

In the context of our computational studies on reactivity of peroxy systems,[14,15] we also addressed the mecha-

(2) (a) Murray, R. W.; Gu, D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 451. (b) Curci, R.; Dinoi, A.; Fusco, C.; Lillo, M. A. *Tetrahetron Lett.* **1996**, *37*, 249. (c) Adam, W.; Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gasparrini, F.; Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkotz, S.; Winde, R. *Chem. Eur. J.* **1997**, *3*, 105 and references therein. (d) Asensio, G.; Mello, R.; Gonzales-Nunez, E.; Boix, C.; Royo, J. *Tetrahetron Lett.* **1997**, *38*, 2373. (e) Gonzales-Nunez, M. E.; Castellano, G.; Andreu, C.; Royo, J.; Baguena, M.; Mello, R.; Asensio, G. *J. Am. Chem. Soc.* **2001**, *123*, 7487. (f) Curci, R.; D'Accolti, L.; Fusco, C. *Tetrahetron Lett.* **2001**, *42*, 7087.

(3) (a) Minisci, F.; Bravo, A.; Fontana, F.; Fronza, G.; Zhao, L. *J. Org. Chem.* **1998**, *63*, 254 and references therein. (b) Vanni, R.; Garden, S. J.; Banks, J.; Ingold, K. U. *Tetrahetron Lett.* **1995**, *36*, 7999.

(4) Simakov, P. A.; Choi, S. Y.; Newcomb, M. *Tetrahetron Lett.* **1998**, *39*, 8187.

(5) (a) Cremer, D.; Kraka, E.; Szalay, P. G. *Chem. Phys. Lett.* **1998**, *292*, 97. (b) CASSCF single-point calculations [(12,10) with the 6-31G-(d) basis set] on the concerted RB3LYP TS **conc-4a** and on the diradicaloid UB3LYP TS **rad,coll-4a** for the reaction of DHD with methane demonstrate that two configurations are present. However, in both cases CI coefficients indicates that one configuration is clearly dominant (TS **conc-4a**: $C_1 = 0.89$ and $C_2 = -0.38$; TS **rad,coll-4a**: $C_1 = 0.86$ and $C_2 = -0.45$), thus making it reasonable the use of the monodeterminantal R(U)B3LYP method. In fact, the configuration coefficients for these two TSs are similar to those found by Kraka and Cremer[5a] for the diradicaloid TS of the ring opening reaction of dioxirane **1-H** to **2-H** ($C_1 = 0.843$ and $C_2 = 0.378$). In this paper the authors stressed that UB3LYP calculations correctly describe the homolytic cleavage of O−O peroxy bond with results "in good agreement with MR-AQCC results".

(6) Aplincourt, P.; Ruiz-Lopez, M. F. *J. Am. Chem. Soc.* **2000**, *122*, 8990.

(7) Anglada, J. M.; Bofill, J. M.; Olivella, S.; Solé, A. *J. Phys. Chem. A.* **1998**, *102*, 3398.

(8) (a) These electrons are housed in the MOs resulting from the bonding and antibonding combinations of the p_z nonbonding orbitals of the oxygen atoms. (b) Ring opening is accompanied by a formal rotation of the two 2p π electron pairs at the O atoms into the OCO plane.

(9) Recently, Fokin et al.[10] have described the radical intermediate **3-Me**, but they only considered the less stable conformer (**anti-3-Me**). Overlooking the more stable conformer can lead, owing to the sizable difference in energy between the two forms, to wrong evaluation of activation and reaction free energy of reactions that involve this species.

(10) Fokin, A. A.; Tkachenko, B. A.; Korshunov, O. I.; Gunchenko, P. A.; Schreiner P. S. *J. Am. Chem. Soc.* **2001**, *123*, 11248. This paper reports the reaction of DMD with highly strained carbon−carbon single bonds that goes through a diradicaloid TS with formation of a diradical intermediate that then fragments to afford the final products.

(11) Bach, R. D.; Glukhovtsev, M. N.; Canepa, C. *J. Am. Chem. Soc.* **1998**, *120*, 10528.

(12) Houk, K. N.; Du, X. *J. Org. Chem.* **1998**, *63*, 6480.

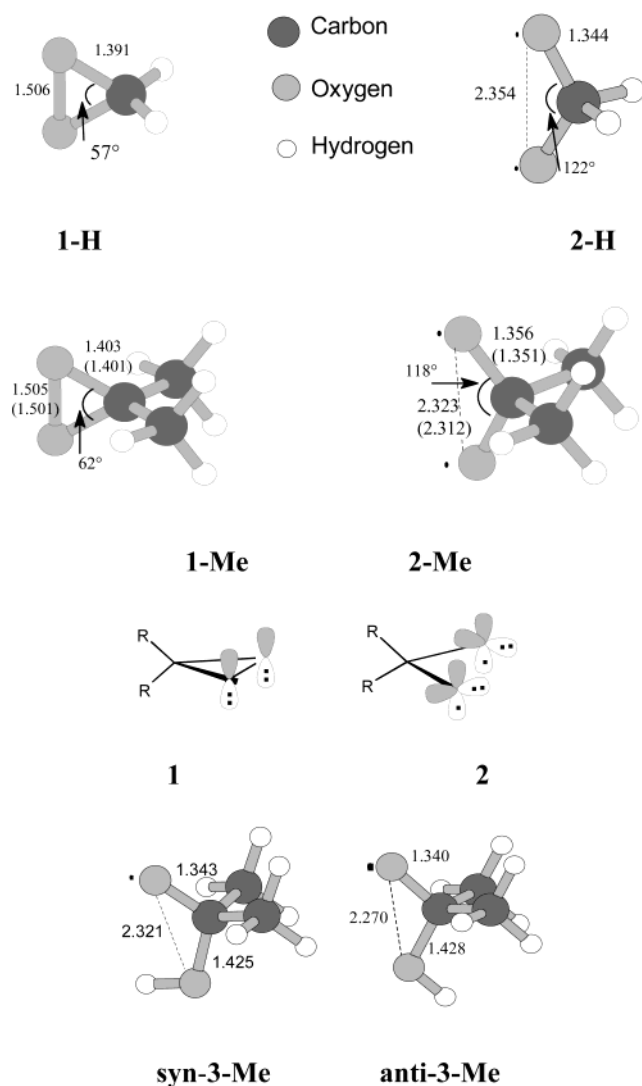(13) Rauk, A.; Shustov, G. V. *J. Org. Chem.* **1998**, *63*, 5413.

FIGURE 1. B3LYP/6-31G(d)-optimized geometries (bond lengths in Å) of dioxiranes (**1-H** and **1-Me**), dioxymethane diradicals (**2-H** and **2-Me**) [B3LYP/6-311+G(d,p) data in parentheses], and the synclinal (**syn-3-Me**) and anti (**anti-3-Me**) isomers of the 2-hydroxyisopropoxy radical. Schematic electronic structure of dioxiranes (**1**) and dioxymethanes (**2**).

nism of oxygen insertion into C—H bonds by dioxiranes by exploring both the concerted mechanism and two conceivable alternative stepwise hypotheses[16] as displayed in Scheme 3. We here report a full account of our DFT study on the reaction of the parent dioxirane (DHD) with methane and of dimethyldioxirane (DMD) with methane, isobutane and acetone. We have also studied the reaction of DHD with ethane, propane, and ethanal and of DMD with ethane and propane, but only a few data for these reactions will be here discussed.

(14) (a) Freccero, M.; Gandolfi, R.; Sarzi−Amadè, M.; Rastelli, A. *Tetrahedron* **1998**, *54*, 6123. (b) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *Tetrahedron* **1998**, *54*, 12323. (c) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M. *Tetrahedron* **1999**, *55*, 11309.

(15) (a) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **1999**, *64*, 3853. (b) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 2030.

(16) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *Tetrahedron Lett.* **2001**, *42*, 2739.
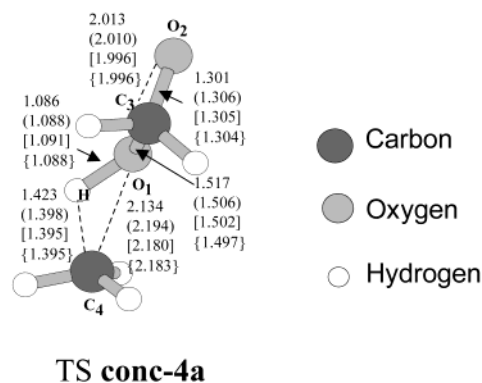
FIGURE 2. B3LYP/6-31G(d)-optimized geometries (bond lengths in Å) of concerted TS (**conc-4a**) [B3LYP/6-311+G(d,p) values in parentheses, B3LYP/aug-cc-pVTZ values in square brackets, and B3LYP/6-311+G(3df,3pd) values in braces] for the oxidation of methane with DHD.

Computational Methods

Hybrid DFT methods, e.g., the B3LYP method, have been shown to properly describe isomerization reactions that involve dioxirane derivatives[5−7] and, in particular, to perform reasonably well also when the multireference problem is present (as in the ring opening of dioxiranes),[5] giving fairly good results in comparison to those obtained with much more sophisticated ab initio methods.[5,6,17,18]

This observation led us to fully optimize transition structures (TSs) of the reactions of DHD with methane (Figure 2) and of DMD with methane, isobutane, and acetone (Figure 3) at both the R(U)B3LYP/6-31G(d) and R(U)B3LYP/6-311+G(d,p) level by using gradient geometry optimization and default threshold for convergence as implemented in the Gaussian 98 suite of programs.[19] (Cartesian coordinates of all reactants and TSs are available in the Supporting Information).

As for the basis set effect, our results demonstrate that geometries of all kinds of TSs do not heavily depend on the basis set used: a slight shift of TSs to an earlier position parallels the extension of the basis set from 6-31G(d) to 6-311+G(d,p) (Figures 2 and 3). Optimization of TS **conc-4a** (for the DHD + methane reaction, Figure 2) with the RB3LYP/aug-cc-pVTZ and RB3LYP/6-311+G-(3df,3pd) methods clearly showed that a further basis set

(17) (a) Grafenstein, J.; Hjerpe, A. M.; Kraka, E.; Cremer, D. *J. Phys. Chem. A* **2000**, *104*, 1748. (b) Foresman, J. B.; Frisch, E. *Exploring Chemistry with electronic structure methods*, 2nd ed.; Gaussian Inc.: Pittsburgh, PA.

(18) (a) Ochoa, E.; Mann, M.; Sperling, D.; Fabian, J. E. *J. Org. Chem.* **2001**, 4223. (b) Staroveror, V. N.; Davidson, E. R. *J. Am. Chem. Soc.* **2000**, *122*, 7377. (c) Hrovat, D. A.; Chen, J.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456. (d) Orlova, G.; Goddard, J. D. *J. Org. Chem.* **2001**, *66*, 4026. (e) Gandolfi, R.; Freccero, M.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 6112.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; 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.; Cioslowski, 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 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

SCHEME 3

4: R=H   **a**: $R_1=R_2=R_3=H$
5: R=Me   **b**: $R_1=R_2=R_3=Me$
              c: $R_1=R_2=H; R_3=COMe$
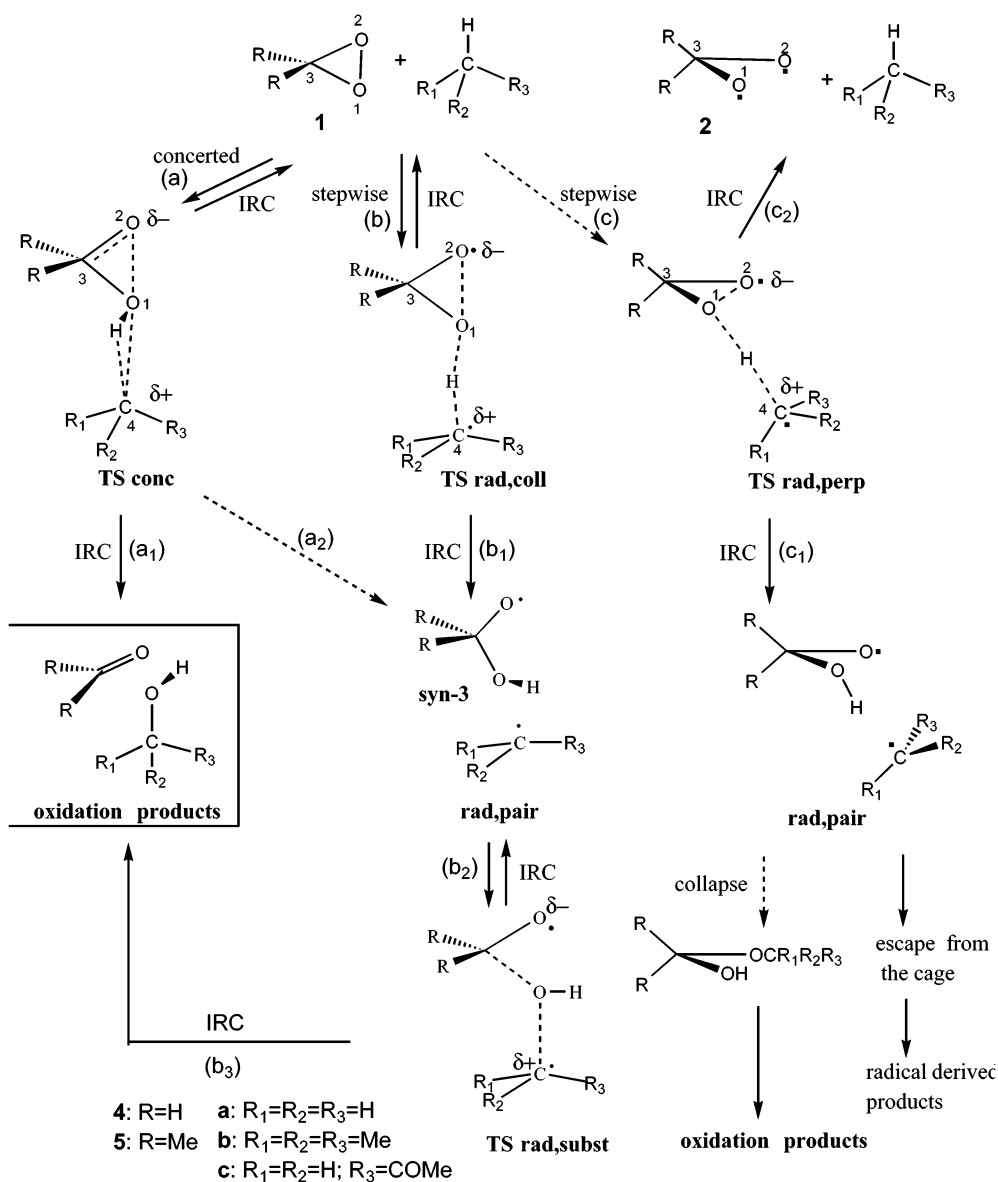
extension leaves TS geometries almost unaltered. In Table 1 only the B3LYP/6-311+G(d,p) geometries are reported and likewise only the geometry data at this level will be used in the discussion.

By contrast the activation energies are appreciably changed as a result of basis set variation from 6-31G(d) to 6-311+G(d,p). Thus, to give an exhaustive description of the energetics we will report and comment on the energy results predicted by both optimization levels.

Furthermore, TSs for the DHD (**conc-4a**) and DMD (**rad,coll-5a** and **rad,perp-5a**) reactions with methane have been located at the R(U)QCISD/6-31G(d) level confirming DFT results (see the Supporting Information).

Critical points have been characterized by diagonalizing the Hessian matrixes calculated for the optimized structures and the wave function stability of all the critical points was checked. All the reported transition structures are first order saddle points with only one negative Hessian eigenvalue (i.e., one imaginary frequency). But while wave functions of all UB3LYP diradi-

caloid TSs for the stepwise mechanisms (TS **rad**)[20] were found to be stable, wave functions of all concerted RB3LYP transition structures (TS **conc**) exhibited an RHF → UHF instability (see Results).

Vibrational frequencies were calculated, under the rigid-rotor harmonic approximation, for optimized B3LYP/6-31G(d) and B3LYP/6-311+G(d,p) structures and were used, unscaled,[21] to compute the zero point energies, thermal corrections to enthalpy, entropy, and Gibbs free energy.

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(20) A problem for the unrestricted methods (UB3LYP) is that wave functions for the optimized singlet open-shell species exhibit spin contamination. For the diradicaloid TSs here reported the ⟨S²⟩ values span the range from 0.4 to 1.0, indicating that singlet wave functions contain substantial amount of the triplet component. The singlet–triplet energy gap is rather low (i.e., of the order of 2 kcal/mol) with the former always more stable. Given that it is not definitely established whether and how B3LYP wave function has to be corrected,[17a] we did not perform energy correction by removing spin contamination. This might mean that the "true" energy of diradicaloid TSs is slightly lower than that here reported.

(21) Rastelli, A.; Bagatti, M.; Gandolfi, R. *J. Am. Chem. Soc.* **1995**, *117*, 4965.
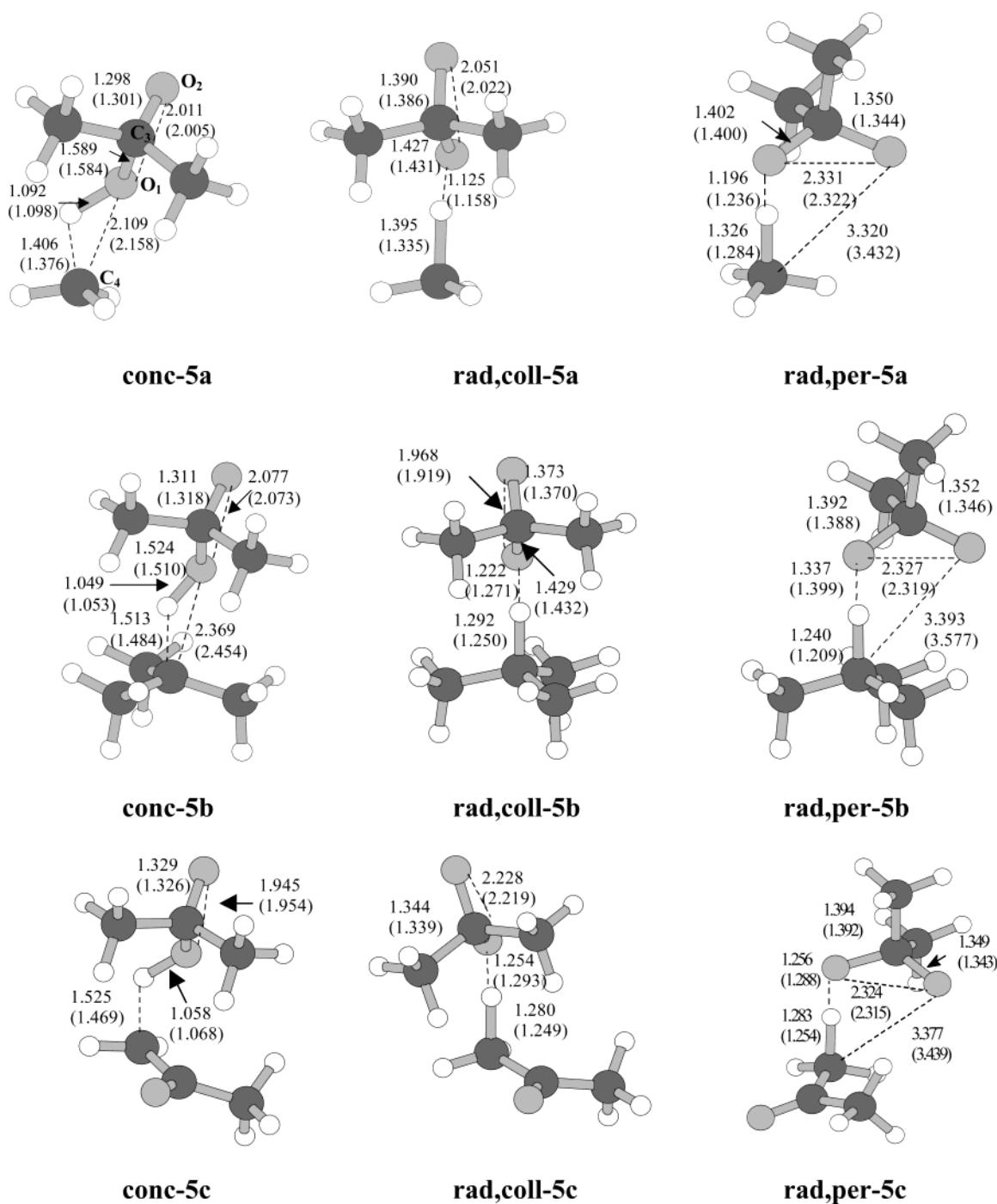
FIGURE 3. R(U)B3LYP/6-31G(d)-optimized geometries [R(U)B3LYP/6-311+G(d,p) values in parentheses] of concerted TSs (**conc-5**) and diradicaloid TSs (**rad,coll-5** and **rad,perp-5**) for the oxidation of methane (a), isobutane (b), and acetone (c) with dimethyldioxirane DMD (bond lengths in Å).

The computed enthalpies, entropies, and Gibbs free energy were converted from the 1 atm standard state into the standard state of molar concentration (ideal mixture at 1 mol/L and 1 atm) since the latter activity scale is generally used for the experimental results in solution.[21,22]

The contribution of solvent (acetone and dichloromethane) effects to the activation Gibbs free energy of the reactions under study were obtained by single point calculations at the B3LYP/6-31G(d) and B3LYP/6-311+G-(d,p) level with the self-consistent reaction field (SCRF) method using the CPCM model.[23]

All IRC calculations were performed at the B3LYP/6-31G(d) level.

(22) Benson, S. Thermochemical Kinetics, Wiley: New York, 1968; p 8.

(23) (a) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161. (b) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (c) Arnaud, R.; Adamo, C.; Cossi, M.; Milet, A.; Vallée; Y.; Barone, V. *J. Am. Chem. Soc.* **2000**, *122*, 324.

TABLE 1. B3LYP/6-311+G(d,p) Geometrical Parameters for Oxygen Insertion into C−H Bonds by DMD

| TS | C_4HO_1 | HO_1O_2 | $O_1C_3O_2$ | μ | CHelpG charges | | | $\langle S^2 \rangle$ | spin density | | |
					alkyl	H	$O_1C(Me)_2O_2$		C_4	O_1	O_2
conc-5a	121.1	146.0	87.4	5.16	0.11	0.30	−0.41				
conc-5b	150.2	154.1	94.1	8.32	0.43	0.15	−0.58				
conc-5c	129.4	140.4	86.1	2.92	0.03	0.31	−0.34				
rad,coll-5a	175.5	156.4	91.7	4.34	0.05	0.30	−0.35	0.70	−0.58	−0.25	0.78
rad,coll-5b	168.9	162.8	86.4	4.90	0.28	0.04	−0.32	0.40	−0.30	−0.22	0.58
rad,coll-5c	176.7	149.2	106.7	2.06	−0.05	0.25	−0.20	1.01	−0.41	−0.54	0.76
rad,perp-5a	179.2	90.6	115.6	1.84	−0.01	0.31	−0.30	0.94	−0.53	−0.45	0.82
rad,perp-5b	169.4	90.3	116.1	1.60	0.24	0.01	−0.25	0.93	−0.32	−0.55	0.80
rad,perp-5c	176.9	90.9	115.6	3.90	−0.06	0.31	−0.25	0.93	−0.41	−0.49	0.81

Moreover, we tested the performance of BLYP and BPW91 pure functionals and results are reported in the Supporting Information.

Results

The Concerted Mechanism. The concerted TS for the reaction of methane with dioxirane, **conc-4a**, has been located with the RB3LYP method, using several basis set (see Figure 2), and at the QCISD/6-31G(d) level (see Supporting Information), while those for the reaction of DMD with methane, isobutane and acetone (TSs **conc-5a**, **conc-5b** and **conc-5c**, respectively) with the 6-31G-(d) and 6-311+G(d,p) basis sets are reported in Figure 3 (see also Table 1 for other RB3LYP/6-311+G(d,p) geometrical parameters).

All the RB3LYP/6-31G(d) TSs exhibit, as previously emphasized also by Bach[11] and Houk,[12] an RHF → UHF wave function instability. In fact, single-point UB3LYP/6-31G(d) calculations on these TSs led to stable wave functions that reside some kcal/mol lower in energy than those obtained by RB3LYP calculations. The RHF → UHF instability, at the B3LYP/6-31G(d) level, of "concerted" TS wave functions increases on going from the methane reaction to those of higher alkanes; namely, it is 0.6, 3.4, 5.3, and 5.7 kcal/mol for the DMD reaction with methane (TS **conc-5a**), propane, isobutane (TS **conc-5b**), and acetone (TS **conc-5c**), respectively, and this trend is nicely confirmed by the data of the DHD reactions with methane (TS **conc-4a**), ethane, propane, isobutane, and ethanal (1.85, 2.8, 4.4, 5.7, and 5.8 kcal/mol, respectively).[24]

One may wonder whether the observed instability of concerted TSs is the result of an artifact of the small 6-31G(d) basis set. Since a better treatment of electron correlation, attainable with larger basis sets, may improve the wave function stability, we located TS **conc-4a** also with B3LYP/6-311+G(d,p), B3LYP/aug-cc-pVTZ, and B3LYP/6-311+G(3df,3pd) methods (Figure 2). The TSs obtained with these larger basis sets are slightly earlier on the reaction coordinate but the corresponding wave functions remain RHF → UHF unstable by 2.6, 2.2, and 2.3 kcal/mol, respectively. Likewise TSs **conc-5a**, **conc-5b**, and **conc-5c** at the B3LYP/6-311+G(d,p) level have an instability very similar (0.8, 5.9, and 5.1 kcal/mol, respectively) to that found with the smaller basis set while, once again, the TS geometries become slightly earlier.

Thus, although very appealing from a mechanistic viewpoint, RB3LYP "concerted" TSs for alkane hydroxylations are seriously flawed by the drawback of wave function instability (as a result of their significant diradical character) and, consequently, cannot be definitely considered genuine transition structures.[17]

Kraka and co-workers have very recently stressed that, if the restricted (DFT) solutions are unstable, restricted calculations have to be replaced by unrestricted (UDFT) procedures,[17a] since the former can lead to errors in geometries as well in energetics.[17] We followed their suggestion, namely, we tried to locate TSs with a geometry very similar to that of the concerted type by optimization with the UB3LYP/6-31G(d) method but all our attempts to locate such TSs failed. That is, we could not locate any stable TS that can directly be connected with both reagents (alkane+dioxirane) and final products (alcohol+ketone) along a concerted one-step pathway.

The Stepwise Mechanisms. The mechanistic debate, summarized in the Introduction, made it mandatory to explore the diradical open-shell potential energy surface and to ascertain whether two-step mechanisms, i.e., "molecule induced homolysis"[25] processes with formation of radical pair intermediates, are viable pathways. Thus, we engaged ourselves in locating TSs for the dioxirane attack on alkane that can likely produce a radical pair. In these TSs, the bonding interaction between O_1 and C_4 must be almost negligible; that is, the C_4−H−O_1 angle must be close to 180°. Two reasonable and appealing attack trajectories that satisfy this criterion feature an orientation of the two reactants in which the C−H alkane bond is either almost "collinear" with or almost "perpendicular" to the dioxirane O−O bond.

The "Collinear" Stepwise Process. Transition structures for the "collinear" approach (path (b) in Scheme 3) were located, with both the UB3LYP/6-31G(d) and UB3LYP/6-311+G(d,p) method, for the reaction of DMD with methane (**rad,coll-5a**), isobutane (**rad,coll-5b**) and acetone (**rad,coll-5c**) (Figure 3). The wave function of all these TSs was found to be stable at both DFT theory levels. They all have the transition vector corresponding to the hydrogen transfer from C_4 to O_1 with concomitant O_1−O_2 breakdown. TS **rad,coll-5a** was located also at the UQCISD/6-31G(d) level substantially confirming DFT geometries.

The most noteworthy geometrical features of these TSs are (i) the tendency of the C_4−H bond to adopt a collinear

(24) Specific and bulk solvation have no appreciable effect on geometry and does not improve wave function stability of TS **conc-5a**. Also the wave function of concerted TS for the reaction of methyl-(trifluoromethyl)dioxirane with methane was found to be instable (see the Supporting Information).

(25) "Molecule induced homolysis" or "molecule induced radical formation" indicate a process in which a radical pair is formed by reaction between two closed shell molecules. Rüchardt, C.; Gerst, M.; Ebenhoch, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1406.
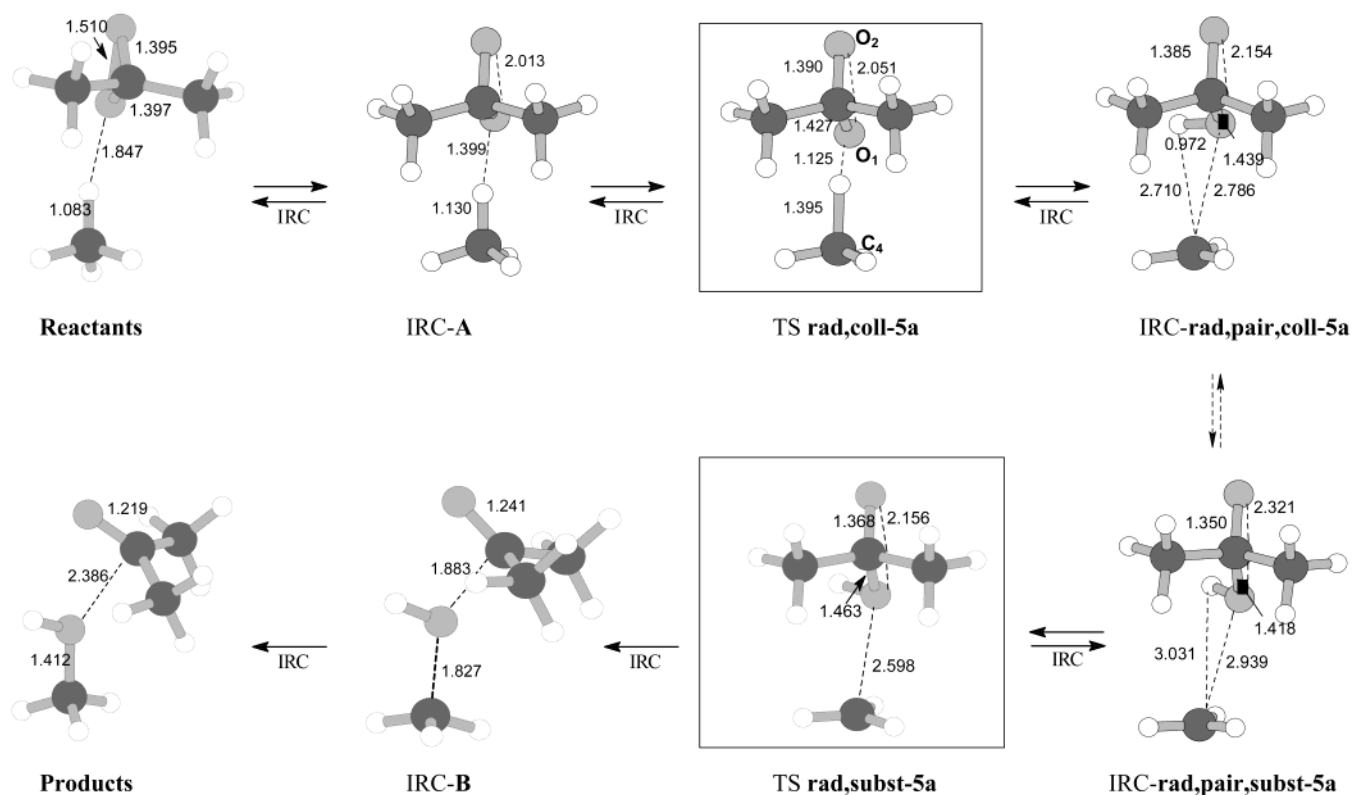
FIGURE 4. Representative UB3LYP IRC points for the oxidation of methane with DMD (bond lengths in Å).

orientation with respect to the O_1-O_2 bond and to lie in the dioxirane plane and (ii) the good alignment of the three atoms directly involved in the H transfer ($\angle C_4-H-O_1 = 169-177°$). The strong widening of the latter angle (by several tenths of degrees, Table 1) represents the most noticeable geometry change observed on passing from TSs **conc** to TSs **rad,coll**. Its value in TSs **rad,-coll** (e.g., $\angle C_4-H-O_1 = 175°$ in **rad,coll-5a**) closely resembles that calculated for the hydrogen abstraction from methane by methoxyl radical,[26] hydroxyl radical ($\angle CH_3-H-OH = 171°$),[27] and cytochrome P450 ($\angle CH_3-H-OFe = 174°$).[28a]

Another relevant difference between TSs **conc** and TSs **rad,coll** is represented by the finding that the H transfer is more advanced in the former than in the latter TSs as shown by breaking C_4- - -H and forming O_1- - -H bond lengths (for example, C_4- - -H = 1.484 Å and O_1- - -H = 1.053 Å for TS **conc-5b** vs C_4- - -H = 1.250 Å and O_1- - -H = 1.271 Å for TS **rad,coll-5b**).

The diradical nature of TSs **rad,coll-5** is supported by the sizable atomic spin density present on C_4, O_1 and O_2 (see Table 1) and by the singlet−triplet spin contamination as revealed by $\langle S^2 \rangle$ values of $\approx 0.4-1.0$. The positive charges (CHelpG, Table 1) on the alkyl fragment, negligible on methyl fragment and significant on *tert*-butyl fragment, are lower than the corresponding charges in concerted TSs. Consistently, dipole moments (Table 1) of **rad,coll** TSs are lower than those of **conc** TSs.

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(26) Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 7821.
(27) Jursic, B. S. *Phys. Lett.* **1996**, *256*, 603.
(28) (a) Ogliaro, F.; Harris, N.; Cohen, S.; Filatov, M.; de Visser, S. P.; Shaik, S. *J. Am. Chem. Soc.* **2000**, *122*, 8977. (b) Musaev, D. G.; Basch, H.; Morokuma, K. *J. Am. Chem. Soc.* **2002**, *124*, 4135.

UB3LYP/6-31G(d) IRC following from TS **rad,coll-5a** toward the reactants led to DMD + methane. Inspection of IRC points (e.g., IRC-**A**, Figure 4) along this way is enlightening as far as timing of O_1-O_2 bond cleavage vs that of the C_4-H bond rupture and the O_1-H bond formation processes is concerned. At IRC-**A** the homolytic dissociation, viewing the process from reactants to TS, of the O_1-O_2 bond is more than half completed, the C_4-H bond rupture is still at its beginning and H- - -O_1 interaction is certainly still weak as suggested by bond lengths and spin densities on the involved atoms. In fact, at IRC-**A** the UB3LYP/6-31G(d) spin density on O_2 is already similar to that at the UB3LYP/6-31G(d) TS (0.73 vs 0.82) while that on O_1 is considerably higher (−0.54 vs −0.24) and, consistently, that on C_4 much lower (−0.24 vs −0.67). All these data nicely conform to a "molecule induced homolysis" mechanism, that is, the collision of methane with dioxirane first brings about the homolysis of the O−O bond while the formation of the H−O_1 bond with the C_4-H concomitant cleavage follows afterward leading directly to the diradicaloid TS **rad,coll-5**.

Thus, we can conclude that the *above results and observations convincingly document the viability of a reaction channel that starting from alkane and dioxirane produces genuine diradicaloid TSs.*

But now what is the fate of TSs **rad,coll**? B3LYP/6-31G(d) IRC following from TS **rad,coll-5a** in the forward direction produced a complex formally consisting of weakly interacting 2-hydroxyisopropoxy (the more stable syn conformer, i.e., **syn-3-Me**) and methyl radicals (IRC-**rad,pair,coll-5a** with spin density of −1.08 at C_4 of the methyl radical and of 0.83 at O_2 of the 2-hydroxyisopropoxy radical, Figure 4 and path (b₁) in Scheme 3). It is

not easy to precisely predict the further evolution of this weak complex. The two components can separate, escape from the cage, and trigger radical side reactions. Alternatively, they can collapse to a hemiketal that in turn decomposes to final products (Scheme 3).[29] The radical–radical recombination must be very fast in order to explain both the experimentally observed configuration retention at an optically active tertiary carbon atom and the results obtained in radical clock studies.[30]

A further path is suggested by the observation that the complex IRC-**rad,pair,coll-5a** is geometrically well disposed to directly enter a homolytic substitution (S_H2) in which the methyl radical attacks the OH group of the 2-hydroxyisopropoxy radical with acetone acting as leaving group (path (b$_2$) in Scheme 3). This type of "oxygen rebound" mechanism has already been proposed by Curci and Adam (see Introduction) as the more appropriate pathway to go from a putative radical pair to final products.

We were able to locate the corresponding TS, that is, **rad,subst-5a** with both the UB3LYP/6-31G(d) (Figure 4) and UB3LYP/6-311+G(d,p) methods.[31] It has an almost pure diradical nature (spin density: −1.02, 0.20 and 0.76 at C_4, O_1, and O_2, respectively; $\langle S^2 \rangle = 0.86$; net charge on $CH_3 \approx +0.05e$) with the C_4- - -OH formation at its very beginning and the C_3–O_1 bond, bound to dissociate, only slightly perturbed. UB3LYP/6-31G(d) IRC analysis downhill from this TS on the forward side led to acetone + methanol (Figure 4 and path (b$_3$) in Scheme 3) while on the reverse side it produced a radical pair (IRC-**rad,pair,subst-5a**, Figure 4) that was similar, even if not coincident, with IRC-**rad,pair,coll-5a**. In the case of the isobutane reaction, the radical pair obtained as the last point of UB3LYP/6-31G(d) IRC calculations, from TS **rad,coll-5b** (Figure 3) in the forward direction, was the complex IRC-**rad,pair,coll-5b** (Figure 5). An easy rotation around the C–OH bond of the 2-hydroxyisopropoxy radical (i.e., from anti to syn conformation) can prepare the OH group to accept the S_H2 attack by the *tert*-butyl radical to afford the fully characterized [with the B3LYP/6-31G(d) method] TS **rad,subst-5b** (Figure 5).

It is useful to emphasize the analogy between the diradical collinear mechanism of alkane hydroxylation by dioxiranes (with the "oxygen rebound" S_H2 process as the last step) and the diradical mechanism of both the Cytochrome P450 and MMO alkane hydroxylation in which, according to recent high-level computational stud-
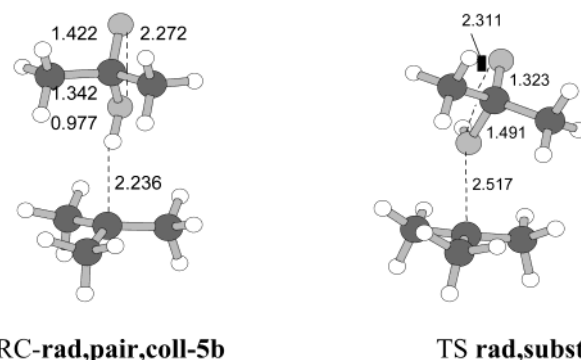

IRC-**rad,pair,coll-5b**   TS **rad,subst-5b**

FIGURE 5. Final point (IRC-**rad,pair,coll-5b**) of UB3LYP/6-31G(d) IRC calculations from TS **rad,coll-5b** and transition structure (TS **rad,subst-5b**) for the final S_H2 step of DMD isobutane oxidation (bond lengths in Å).

ies (by Shaik et al.[28a] and Morokuma et al.,[28b] respectively) the hydrogen abstraction phase is followed by an "oxygen rebound" S_H2 process.

An overview of the energetics of the collinear stepwise route for methane and isobutane reaction is displayed in Figure 6. We evaluated the activation parameters of the S_H2 step with reference to the fully optimized components of the radical pair and by choosing the more stable conformer, i.e., **syn-3-Me**, for the 2-hydroxy isopropoxy radical. This choice led to an electronic activation barrier [UB3LYP/6-311+G(d,p) data, Figure 6] of 6.2 kcal/mol for the methane reaction (TS **rad,subst-5a**) while this value falls down to 0.4 kcal/mol for the isobutane reaction (TS **rad,subst-5b**). The latter value supports the feasibility of a very fast S_H2 process for optically active tertiary radicals in agreement with experimental data (e.g., configuration retention at the tertiary center). However, treating the two diradicals as fully free particles, that is, taking into account the large negative activation entropy that characterizes intermolecular reactions between two free particles, gives rise to Gibbs free activation energy (in acetone solution) of 13.5 and 8.4 kcal/mol, respectively, for the methane and isobutane reaction. Unfortunately, the latter values are not compatible with experimental data. Nevertheless, if the two radical moieties always maintain a weak interaction between each other (i.e., the two radicals form a bound radical)[32] the system might reach TS **rad,subst-5** without having to pay any entropy cost.

Finally, one can also argue that the very low activation energy of the S_H2 step (for alkyl polisubstituted carbon centers) might well disappear, e.g., as a result of more sophisticated calculations.[33] The diradical pair would not represent any more a minimum but only a nonstationary point on the PES downhill to the products. That is, be this the case, the two-step nonconcerted process would become a one-step but still nonconcerted mechanism[34] with the diradicaloid TS that collapses directly to products without formation of any intermediate. This kind

(29) Hemiketal intermediates could never be detected experimentally.[1,2] One can reasonably argue that their decomposition should be faster than their formation, however, as suggested by a referee, further careful control experiments are in order given that this point is critical for the "perpedicular" mechanism.

(30) The "oxygen rebound" via recombination of the two radical centers can take place within the solvent cage practically with no barrier but the two fragments, as they are formed in IRC-**rad,pair,coll-5a**, are not properly oriented for coupling and some reorientation is necessary to allow fast bond formation. Newcomb et al. suggested, on the basis of radical clock experiments, that the maximum lifetime of a possible radical pair is of the order of 0,2 picoseconds.[4] During such a short time the two radicals must reorient and their radical centers must approach to each other at a distance of ≈ 3 Å so that bonding can begin. This task might probably be achieved only if the energy delivered on the descent from the TS concentrates in the appropriate degree of freedom.

(31) As usual the geometry obtained with the larger basis set is slightly earlier than that with the lower one (e.g., C_4- - -O_1=2.661 Å; O_1–C_2 = 1.464 Å; C_2–O_1 = 1.371 Å).

(32) A mechanism that looks like this one has been advanced for alkane hydroxylation with methane monooxygenase on the basis of molecular dynamic simulations. Guallar, V.; Gherman, B. F.; Miller, W. H.; Lippard, S. J.; Friesner, R. A. *J. Am. Chem Soc.* **2002**, *124*, 3377.

(33) For example, as suggested by a reviewer, the energy minimum that corresponds to the radical pair might be the result of an overestimation of its stability by the UB3LYP method.
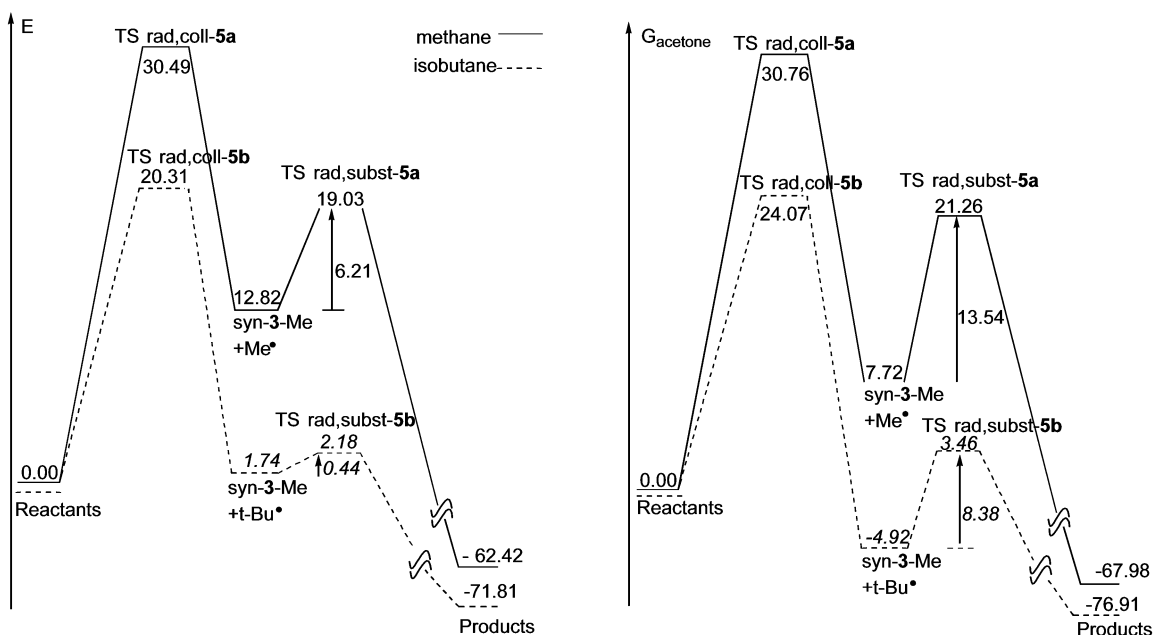
FIGURE 6. B3LYP/6-311+G(d,p) energy profile [kcal/mol, electronic energy (left) and Gibbs free energy in acetone solution (right)] for the collinear stepwise route for methane and isobutane oxidations by DMD. Data for TS **rad,subst-5b** (in italic) are from B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) calculations.

of mechanism has recently been reported for oxygen insertion into C−H bond by trifluoroperoxyacetic acid.[35]

The "Perpendicular" Stepwise Route. The UB3LYP search led us to locate also another kind of diradicaloid TS, namely, the "perpendicular" TS exemplified by **rad,-perp-5a**, **rad,perp-5b**, and **rad,perp-5c** located for the DMD oxidation of methane, isobutane, and acetone, respectively, at both the UB3LYP/6-31G(d) and UB3LYP/6-311+G(d,p) levels (Figure 3 and Table 1). Moreover, TS **rad,perp-5a** has been located also at the UQCISD/6-31G(d) level (see the Supporting Information). These genuine first-order saddle points, with stable wave function, exhibit only one imaginary frequency corresponding mostly to the hydrogen transfer from C_4 to O_1. In TSs **rad,perp** there is a good alignment of O_1, H, and C_4 atoms [$<O_1-H-C_4 = 179°$ in **rad,perp-5a**] with the H-transfer trajectory very close to being perpendicular to the O_1- - -O_2 bond axis ($<O_2-O_1$- -C_4 and $<O_2$- - -O_1- $H \approx 90°$) and it is inclined outside with respect to the dioxirane plane (Scheme 3 and Figure 3). The O_1- - -O_2 bond length (2.322 Å in **rad,perp-5a** vs 2.022 Å in **rad,-coll-5a** and 2.005 Å in **conc-5a**) and the value of the $\langle O_1-C_3-O_2$ angle (116° in **rad,perp-5a** vs 92° in **rad,-coll-5a** and 87° in **conc-5a**) suggest that the O_1-O_2 bond breaking is already completed at the TS. In fact, in TSs **rad,perp** the geometry of the former dioxirane fragment closely resembles that of the ground-state open dioxirane,
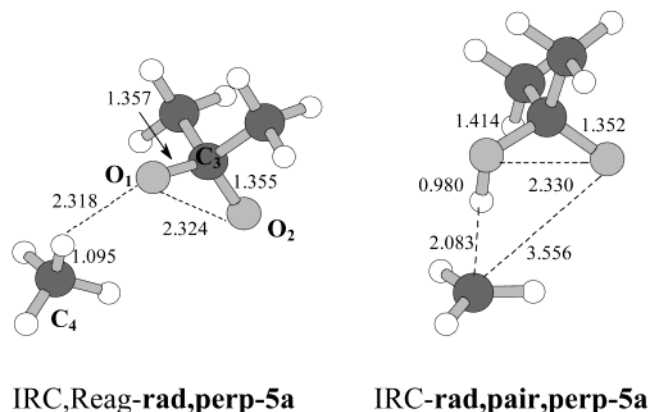
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(34) (a) In this context, it is appropriate to emphasize that the designation of "concerted" for the TSs **conc** (e.g., TSs **conc-4** and **conc-5**), on the basis of the timing in C_4-O_1 vs O_1-H formation, is probably not fully adequate. Actually, a better description of the mechanism with the almost completely formed O_1-H vs the still weak bonding interaction between C_4 and O_1 (the two reference processes) in **conc** TSs would be (according to Lowe's suggestion)[34b] that of a one step (that is, without intermediates) borderline between concerted and non concerted mechanism. (b) Lowe, J. P. *J. Chem. Educ.* **1974**, *51*, 785.

(35) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *Tetrahedron* **2001**, *57*, 9843.

IRC,Reag-**rad,perp-5a**   IRC-**rad,pair,perp-5a**

FIGURE 7. Final geometry of UB3LYP/6-31G(d) IRC calculations starting from TS **rad,perp-5a** toward reactants and products, respectively, for the reaction of dimethyldioxirane with methane (bond lengths in Å).

namely, the π,π-dioxymethane diradical **2** (**2-Me**: $\langle O_1-C_3-O_2 = 118°$ and O_1- - -$O_2 = 2.312$ Å). The diradical nature of TSs **rad,perp** is corroborated by the noticeable atomic spin density (Table 1) present on C_4 (−0.53 for **rad,perp-5a**), O_1 (−0.45) and O_2 (0.82). The dipole moments of TSs **rad,perp** are lower than those of TSs **rad,coll** that in turn are smaller than those of TSs **conc**. The net electron transfer (Table 1) from the alkane to dioxirane demonstrates that the attack by dioxiranes on alkanes keeps on being electrophilic not only in the radical collinear but also in the radical perpendicular mechanism.

UB3LYP/6-31G(d) IRC calculations demonstrated that TS **rad,perp-5a** is connected (path (c_1) in Scheme 3) to a singlet radical pair (IRC-**rad,pair,perp-5a** in Figure 7) consisting of methyl and 2-hydroxyisopropoxy radicals. It is interesting to note that, in contrast with IRC-**rad,-pair,coll-5a**, this singlet radical pair is not ideally

TABLE 2. Gas-Phase[a] and Solution (Dichloromethane and Acetone, $\Delta G^{\ddagger}_{sol}$)[b-d] Activation Parameters for TSs 5 at the B3LYP/6-31G(d) and B3LYP/6-311+G(d,p) Levels

	B3LYP/6-31G(d)						B3LYP/6-311+G(d,p)					
	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{sol}{}^{c}$	$\Delta G^{\ddagger}_{sol}{}^{d}$	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{sol}{}^{c}$	$\Delta G^{\ddagger}_{sol}{}^{d}$
Conc-5a	45.83	44.02	−15.77	48.74	46.98	46.38	39.06	37.22	−18.18	42.65	40.36	39.79
Conc-5b	31.97	29.81	−22.01	36.39	33.77	32.59	24.18	21.69	−20.31	27.75	23.22	21.93
Conc-5c	39.31	37.96	−29.55	46.25	48.53	47.94	34.71	33.07	−28.03	40.78	43.15	42.63
Rad,coll-5a	36.06	32.33	−15.75	37.04	37.25	36.79	30.49	26.93	−14.58	31.29	31.16	30.76
Rad,coll-5b	24.52	21.32	−22.12	27.93	29.05	28.23	20.31	17.59	−21.27	23.94	24.81	24.07
Rad,coll-5c	26.27	22.19	−26.98	30.19	34.01	33.47	22.89	19.46	−24.98	26.27	30.22	29.81
Rad,perp-5a	27.85	24.06	−17.90	29.41	30.78	30.45	22.84	19.22	−17.28	24.39	25.74	25.50
Rad,perp-5b	19.18	15.71	−23.42	22.71	25.84	25.24	15.83	12.62	−21.82	19.14	22.51	22.01
Rad,perp-5c	21.96	18.47	−26.27	25.67	29.40	28.91	18.72	15.30	−25.80	22.35	26.29	25.93

[a] Barrier heights are relative to **1-Me** and alkane. Energies in kcal/mol, entropy in cal/mol K; standard state (298.15 K) of the molar concentration scale (gas in ideal mixture at 1 mol/L, $P = 1$ atm).[21,22] Statistical effects included. [b] Solvent effect evaluated with the COSMO model. [c] Dichloromethane. [d] Acetone.

oriented for an S_H2 rebound process but it can enter the barrierless recombination of its radical centers to give 2-methoxy-2-propanol without considerable reorientation of its components. That is, components of IRC-**rad,pair,-perp-5a** may separate and escape from the cage, can reorient themselves and enter S_H2 reaction but a very fast rebound to give methoxy-2-propanol should certainly be the largely preferred pathway.[29]

But now, does TSs **rad,perp-5** originate directly from alkane and DMD? The answer of IRC analysis is no. In fact starting from **rad,perp-5a** and following the reaction coordinate in the reactant direction led to a complex between methane and π,π-dioxymethane diradical **2-Me** (IRC,Reag-**rad,perp-5a** in Figure 7 and path (c₂) in Scheme 3). Consequently, this IRC finding suggests that TSs **rad,perp** derive from attack of π,π-dioxymethane diradicals **2** (formed from unimolecular ring opening of dioxiranes **1**) on alkanes but the question arises whether this mechanism can actually be operative. High-level computational evidence by Cremer et al.[5a] and Anglada et al.[7] suggest that compounds **2** once formed should rapidly produce the corresponding rearranged carboxyl derivatives (formic acid and methyl acetate, respectively, for **2-H** and **2-Me**) with very low barriers [$\Delta E^{\ddagger} \approx 4$ kcal/mol at the B3LYP/6-31(d,p) level][5a] so that **2** cannot be intercepted in a bimolecular reaction.[36,37] It is quite evident that oxygen insertion cannot derive from the reaction of the free preformed **2**.

However, IRC calculations do not definitely eliminate the possibility that a perpendicular collision between dioxirane and alkane triggers a "molecule induced homolysis" directly producing TS **rad,perp**[38] and, for sake

of comparison, in the next section we will assume that also this reaction pathway originates from alkane and dioxirane.

Activation Barriers for the Competing Processes of Alkane Oxidation with Dioxiranes. At this point, it is interesting to compare the activation parameters for the diradicaloid TSs (**rad,coll** and **rad,perp**, UB3LYP calculations) with those for the corresponding concerted TSs (**conc**, RB3LYP calculations) to evaluate (i) whether the former mechanisms can really compete, on energetic grounds, with the latter one and (ii) to what extent the different mechanisms are consistent with the known experimental data. Activation parameters are collected in Table 2 (all parameters are referred to dioxirane + alkane), which gathers the data for the reactions of DMD with methane, isobutane and acetone at the R(U)B3LYP/6-31G(d) and R(U)B3LYP/6-311+G(d,p) level.

Methane Reaction. For the methane reaction diradicaloid TSs **rad,coll-5a** and **rad,perp-5a** are highly favored at the B3LYP/6-31G(d) level over the corresponding concerted TS **conc-5a**. Neither basis set extension nor solvent effects do dramatically change the predictions for competition between concerted and stepwise mechanisms for DMD oxygen insertion into methane C−H bonds (Table 2).

Isobutane Reaction. Replacement of H atoms of methane by methyl groups, i.e., passing to isobutane reaction, brings about a very strong reduction in the activation energies for the concerted process owing to the high ability of the *tert*-butyl fragment in stabilizing a positive charge (the net positive charge on the *tert*-butyl moiety of TS **conc-5b** is +0.43 while it is quite small on the methyl moiety of TS **conc-5a**): RB3LYP/6-31G(d) calculations predict a decrease in the electronic activation energy, for TS **conc-5b** with respect to TS **conc-5a**, of 14 kcal/mol that becomes slightly larger (15 kcal/mol) at the RB3LYP/6-311+G(d,p) level.

One can anticipate that alkyl substitution effect should be less pronounced in diradicaloid TSs.[39] Actually, at the UB3LYP/6-31G(d) level the predicted reduction, on going from methane to isobutane, in electronic activation energy is of 11.5 and 8.7 kcal/mol, respectively, for the collinear and perpendicular radicaloid attacks. Moreover the accelerating effect due to methyl substitution falls

(36) For example, at the B3LYP/6-31G(d,p)//B3LYP/6-31G(d) level, the reaction of **2-Me** with isobutane via TS **rad,perp-5b** is certainly much slower ($\Delta E^{\ddagger} = 3.26$ kcal/mol, $\Delta H^{\ddagger} = 1.32$ kcal/mol, $\Delta S^{\ddagger} = -25.40$ e.u. and $\Delta G^{\ddagger} = 8.91$ kcal/mol) than the unimolecular rearragement. Moreover, the calculated **1-Me**→ **2-Me** ring opening energy [25 kcal/mol at the B3LYP/6-31G(d) level][5a] reproduces very well the experimental value (24.9 kcal/mol).[37] Consequently in a mechanism with the **1** → **2** ring opening followed by the attack of **2** on alkane, the former unimolecular reaction would be the rate determining step in striking contrast with the observed second-order kinetics and isotope effects.

(37) Hull, L. A.; Buhai, L. *Tetrahedron Lett.* **1993**, *34*, 5039.

(38) One should remember that IRC traces the minimum energy path and not real trajectories. Consequently, it is not surprising that IRC following from TS **rad,perp-5** (the dioxirane moiety of which exhibits a geometry very similar to that of **2**) toward the reactants moves along the path that involves minor electronic and geometric changes, namely that one leading to **2** plus methane. Only molecular dynamic studies can probably shed light on the possible direct origin of TS **rad,perp** from reactants.

(39) March, *J. Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley-Interscience: 1985; pp 146 and 166.
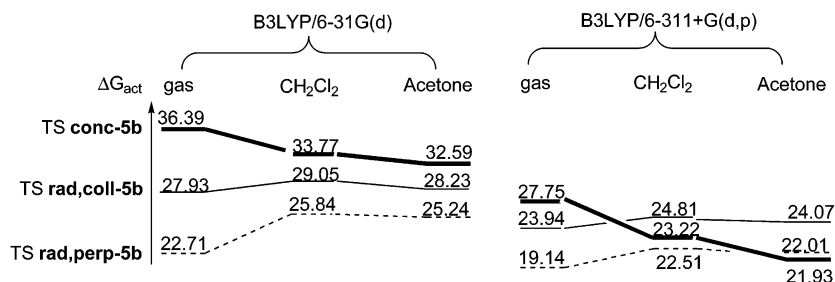
FIGURE 8. Schematic representation of basis set and solvent effects on the competition between concerted and diradical mechanisms for the DMD oxidation of isobutane.

down to 10.2 and 7.0 kcal/mol, respectively, by using the UB3LYP/6-311+G(d,p) method. As a result, in the case of isobutane reaction in gas phase the diradicaloid TSs continue to be favored over the concerted one but now the activation Gibbs free energy gap (B3LYP/6-311+G-(d,p), $G^{\ddagger}_{rel}$ for TS **conc-5b**, **rad,coll-5b**, and **rad,perp-5b**: 0.00, −3.8, and −8.6 kcal/mol, respectively) is much lower than for methane oxidation.

An important factor that strongly influences competition between the stepwise and concerted mechanisms of the isobutane reaction with DMD is represented by solvent effects. Actually, the solvent effect on activation energies is opposite for the diradical perpendicular route in comparison with the concerted one. For example, according to B3LYP/6-311+G(d,p) calculations, the reaction rate of the stepwise channel via **rad,perp-5b** should be significantly retarded on passing from gas phase to acetone solution ($\Delta G^{\ddagger}_{sol} - \Delta G^{\ddagger}_{gas} = 2.9$ kcal/mol) while a relevant rate acceleration ($\Delta G^{\ddagger}_{sol} - \Delta G^{\ddagger}_{gas} = -5.8$ kcal/mol) is predicted for the concerted insertion and the reaction rate constant should be almost unchanged for the collinear process via TS **rad,coll-5b**. This finding is consistent with the dipole moment ranking of competing TSs: **conc-6b** > **rad,coll-6b** > **rad,perp-6b**.

The different sensitivity of the three mechanisms to solvent effects dramatically changes the competition among the different paths for DMD oxygen insertion into tertiary isobutane C−H bond on passing from gas phase to solution. According to B3LYP/6-31G(d) data the stepwise mechanisms remain clearly favored over the concerted path also in solution but the reactivity gap is strongly reduced with respect to the gas phase (Table 2 and Figure 8). At the B3LYP/6-311+G(d,p) level, the activation free energies in solution are compressed in a small range and some reactivity reversal is predicted in acetone solution. In fact at the latter theory level TS **conc-5b** and TS **rad,perp-5b**, on the assumption that the "molecule induced homolysis" mechanism is viable for the perpendicular channel, compete in a substantially balanced way and both prevail over TS **rad,coll-5b** ($G^{\ddagger}_{rel,sol}$ for TS **conc-5b**, **rad,coll-5b**, and **rad,perp-5b**: 0.00, 2.1, and 0.1 kcal/mol, respectively).[40]

As for consistency of the theoretical reactivity data for the different mechanisms with the experimental findings,

the activation free energies obtained at the higher calculation level in acetone for TS **conc-5b** ($\Delta G^{\ddagger} = 21.9$ kcal/mol) and TS **rad,perp-5b** ($\Delta G^{\ddagger} = 22.0$ kcal/mol) compare very well with the experimental datum for the reaction of DMD with 1,2-cis-dimethylcyclohexane (21 kcal/mol)[2c] while that for **rad,coll-5b** ($\Delta G^{\ddagger} = 24.1$ kcal/mol) is only slightly worse.

Another interesting point is the observation that tertiary C−H bond can be attacked by DMD in a chemospecific (or highly chemoselective) reaction in the presence of secondary C−H bond ($\Delta\Delta G^{\ddagger} > 2.5$ kcal/mol in acetone solution).[41] The higher reactivity of tertiary vs secondary C−H bonds predicted by UB3LYP/6-311+G-(d,p)//UB3LYP/6-31G(d) calculations for the diradical perpendicular processes [e.g., the difference in stability of the TS of propane reaction with DMD as compared to **rad,perp-5b** of isobutane reaction] is too small ($\Delta G^{\ddagger}_{propane} - \Delta G^{\ddagger}_{isobutane} = 0.4$ kcal/mol in acetone solution)[42] to match the experimental finding. The computed data for the diradical collinear processes compare slightly better ($\Delta G^{\ddagger}_{propane} - \Delta G^{\ddagger}_{isobutane} = 1.1$ kcal/mol for DMD oxidation in acetone solution) but are still unsatisfactory whereas those for the concerted processes ($\Delta G^{\ddagger}_{propane} - \Delta G^{\ddagger}_{isobutane} = 4.9$ kcal/mol in acetone solution) explain very well this reactivity aspect.

Reaction with Acetone and Competition between Acetone and Isobutane. Table 2 allows one to compare the energetics of TS **conc-5c** vs those of the diradicaloid transition structures for the collinear (**rad,coll-5c**) and perpendicular (**rad,perp-5c**) approach of the reaction of DMD with acetone: at all theory levels, both in the gas phase and in solution, the diradicaloid TSs strongly overwhelm the concerted TS while TS **rad,perp-5c** is favored by 4−5 kcal/mol over TS **rad,coll-5c**.

An important point, which allows one to test the reliability of the computed stepwise and concerted mechanisms, is the possible competition between acetone and the alkane tertiary C−H bond. Oxygen insertion reac-

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(40) Very similar solvent effects were obtained with the IEFPCM method. However, the very interesting results on solvent effects must be taken with some caution. For example, our calculations predict a higher reactivity in acetone than in dichloromethane while experimental data indicate that the hydroxylation of 1,2-dimethyl cyclohexane by DMD is two times faster in dichloromethane than in acetone solution.[2a]

(41) The reaction of adamantane with DMD represents the only example in which secondary C−H compete to some extent with tertiary C−H bond (under typical reaction conditions 1-AdOH (91.5%) was accompanied by very small amounts (1%) of 2-AdOH).[2b] A referee suggested that reaction of secondary C−H bond could represent an artifact due to the onset of radical DMD decomposition over the long reaction times. As a rule, e.g., reactions of DMD with 1,2-dimethyl-cyclohexanes and decalins, only attack at the tertiary C−H was observed.

(42) Activation parameters (kcal/mol) for propane reaction with DMD at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) TS **conc**: $\Delta E^{\ddagger} = 28.58$, $\Delta G^{\ddagger} = 32.98$, $\Delta G^{\ddagger}_{acetone} = 29.77$; TS **rad,coll**, $\Delta E^{\ddagger} = 21.94$, $\Delta G^{\ddagger} = 24.75$, $\Delta G^{\ddagger}_{acetone} = 24.81$; TS **rad,perp**, $\Delta E^{\ddagger} = 16.76$, $\Delta G^{\ddagger} = 20.18$, $\Delta G^{\ddagger}_{acetone} = 22.24$.

tions with DMD into C−H bond can satisfactorily be carried out in acetone solution with good yields and no competition with the insertion into acetone C−H bonds has, to the best of our knowledge, been reported to date. Consequently, the reaction rate constant predicted for a mechanism of oxygen insertion into alkane tertiary C−H bond should be much higher than that into RCOCH$_2$−H bond in order to be compatible with the presence of acetone as solvent, given also that under these conditions concentration effects strongly favor acetone over alkane.

Inspection of Table 2 clearly shows that the concerted mechanism very well explains the experimental observations since the concerted oxidation of acetone by DMD has to surmount a free activation energy that is more than 10 kcal/mol higher than $\Delta G^{\ddagger}$ of the corresponding oxidation of isobutane tertiary C−H.[43] The diradical collinear oxygen insertion into tertiary C−H bond is favored over that into MeCOCH$_2$−H by 2−3 kcal/mol at the potential energy level and this gap increases to 5−6 kcal/mol when the free activation energy in acetone is considered. In the perpendicular stepwise process the alkane reaction overcomes the acetone reaction by ≈ 3 kcal/mol at the potential energy level and by ≈ 3.8 kcal/mol at the free energy level in acetone. Thus, the collinear stepwise process seems to be, on the basis of calculated $\Delta G^{\ddagger}$ in solution, compatible with acetone as solvent but in the case of the perpendicular mechanism the difference in reactivity between tertiary alkane and acetone does not appear large enough to completely avoid competition with the solvent.

Conclusion

In summary, we have carefully studied the dioxirane (parent dioxirane and dimethyldioxirane) hydroxylation of C−H bonds (of methane, isobutane and acetone) with the DFT theory, using both restricted and unrestricted B3LYP methods with 6-31G(d) and 6-311+G(d,p) basis set to evaluate the feasibility of stepwise mechanisms and their competition with the concerted counterpart.

In the first part of the paper, we have stressed that there are theoretical problems for the concerted mechanism. Actually, all concerted TSs located by us and, previously, by other authors with the RB3LYP method exhibit an RHF→ UHF wave function instability that casts some doubt on the precise nature of these TSs. Actually, no TSs with a geometry strictly similar to that of concerted TSs could be located by the more adequate UB3LYP method. This is a real pity as the concerted mechanism convincingly explains the most important experimental observations such as configuration retention at the chiral centers, the result of radical clock studies, the higher reactivity of tertiary C−H as compared to secondary C−H bond and the compatibility of acetone as solvent in dioxirane hydroxylations.

Meanwhile, we were able to characterize, with UB3LYP methods, two possible two-step processes that can produce the final products via singlet radical pairs. For the first step of these mechanisms we managed to locate two kinds of genuine diradicaloid TSs, namely, TSs **rad,coll** and **rad,perp** that exhibit one imaginary frequency and

have stable wave functions. These two kinds of TSs differ in the approach geometry between reactants. In TSs **rad,coll** the alkane C−H bond tends to be collinear with the breaking O$_1$- - -O$_2$ bond and to lie in the plane of the dioxirane ring. In TSs **rad,perp** the alkane C−H bond is almost perpendicular to the O$_1$- - -O$_2$ bond, it is located out of the plane of the dioxirane ring and it is inclined outside (away from the RRC moiety of the dioxirane ring).

IRC analysis clearly demonstrates that TSs **rad,coll** are connected, on the reverse side, to dioxirane+alkane and that their formation represents a nice computational example of "molecule induced homolysis" reaction: collision between alkane and dioxirane (closed shell species) brings about the homolytic breaking of the dioxirane O−O bond and the hydrogen abstraction follows afterward to produce the singlet diradical TSs **rad,coll**. These TSs are connected, on the forward side, to a singlet radical pair complex that has an ideal orientation to proceed further along the pathway and directly furnish the final products via a fast S$_H$2 reaction. Alternatively, reorientation of the radical pair components opens the way to a barrierless recombination of the two radical centers to give a hemiketal that in turn can decompose to final products. Finally, the hypothesis that the radical collinear TSs may collapse directly to products in a "one-step nonconcerted" process has been discussed.

The TS **rad,perp** is not connected, according to IRC analysis, with dioxirane + alkane but with singlet diradical dioxymethane + alkane. However, a preliminary ring opening to give the dioxymethane diradical that then reacts with the C−H bond is not consistent with the computationally predicted very high unimolecular rearrangement rate of dioxymethane diradical. A possible direct production of TSs **rad,perp** from a collision between the reactants cannot be definitely excluded. IRC following from the TSs **rad,perp** in the forward direction leads to a singlet radical pair intermediate that is adequately oriented to very rapidly collapse to the hemiketal (and then to final products).

TSs **rad,coll** and **rad,perp** do not satisfactorily explain the well-known very high selectivity of dioxirane attack on tertiary C−H in the presence of secondary C−H bonds that is well rationalized by TSs **conc**.

As for compatibility of stepwise mechanisms with acetone as solvent, calculations suggest that the rad,coll route can withstand acetone as solvent while in a perpendicular radical attack the alkane tertiary C−H bond is not reactive enough to fully overcompensate for concentration effects that favor acetone.

Finally, were all of three mechanisms contemporarily operative, the TS free energy ranking for DMD reactions is as follows:

(i) for the hydroxylation of methane and acetone C−H bond, the radicaloid TSs reside at considerably lower energy than the concerted TS with the TS **rad,perp** that is favored by 4−5 kcal/mol over TS **rad,coll** at all theory levels and both in gas phase and in solution; (ii) for the hydroxylation reaction of isobutane tertiary C−H bond, the TS **rad,perp** and TS **conc** should compete each other on the same foot and prevail (by 2 kcal/mol) over the corresponding TS **rad,coll** in acetone solution according to predictions at the B3LYP/6-311+G(d,p) level. This stands in contrast with predictions at the same theory level but for gas-phase reaction where TS **rad,perp**

(43) Rauk et al.[13] have already emphasized, by studying the reaction of DHD with acetaldehyde (as model for acetone), that the presence of acetone as solvent is compatible with the concerted mechanism.

should prevail over TS **rad,coll** that in turn should clearly overcome TS **conc**. That is, solvation highly favors the concerted mechanism over its stepwise counterparts. A lower theory level B3LYP/6-31G(d) is detrimental for the concerted process that both in gas phase and (even if with a lower gap) in solution should not be competitive with stepwise paths.

Supporting Information Available: B3LYP electronic energies and Cartesian coordinates of all reactants and TSs are reported. BLYP and QCI data are included and discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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