# Oxyfunctionalization of Non-Natural Targets by Dioxiranes. 6. On the Selective Hydroxylation of Cubane

Cosimo Annese,[†] Lucia D'Accolti,[†] Caterina Fusco,[†] Remo Gandolfi,[‡] Philip E. Eaton,[*,§] and Ruggero Curci[*,†,||]

Dipartimento Chimica, CNR.-ICCOM, Università di Bari, v. Amendola 173, I-70126 Bari, Italy, Dipartimento di Chimica Organica, Università di Pavia, v.le Taramelli 10, 27100 Pavia, Italy, Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, and Department of Chemistry, Brown University, Providence, Rhode Island 02912

curci@ba.iccom.cnr.it; eaton@uchicago.edu

ABSTRACT
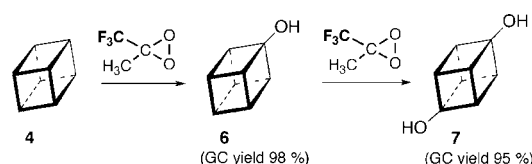
By using methyl(trifluoromethyl)dioxirane (TFDO), the direct mono- and bishydroxylation of cubane could be achieved in high yield under remarkably mild conditions. Comparison of the rates of dioxirane O-insertion with those of standard reference compounds, such as adamantane and cyclopropane, as well as ab initio computations provide useful hints concerning the mechanism of these transformations.

In the last decades, the direct oxyfunctionalization of "unactivated" C−H bonds using dioxiranes (**1**)[1,2] has opened an important new area of oxidation chemistry. The efficient hydroxylation of simple and/or structurally complex alkanes under mild conditions is the highlight of the chemistry of these extraordinarily effective oxidants. These transformations are earmarked by high selectivity, and tertiary C−H bonds are considerably more reactive toward dioxirane O-insertion than secondary or primary units.[2,3]

As a result, high tertiary vs secondary selectivities (R_s^t from 15 to over 250) can be routinely achieved.[4]

The selective hydroxylation of adamantane (**2**) by dioxiranes **1a** (DDO) and **1b** (TFDO) to yield adamantan-1-ol is illustrative. With the powerful methyl(trifluoromethyl)dioxirane (**1b**) in excess, the all-bridgehead hydroxylated tetraol **3** is obtained in 73% yield[4] (Figure 1).

In these oxidations, kinetic data have shown that TFDO is more reactive than DDO by a factor of almost 10^3, with no loss of selectivity. This and many other facets of alkane oxyfunctionalization using dioxiranes have been discussed in a recent account.[4]

We have investigated the reactivity of a few strained polycyclic hydrocarbons having a peculiar architecture, i.e., 2,4-didehydroadamantane[1] and BinorS,[5] along with bicyclics that function as fast radical-clock probes.[4]

[†] Università di Bari.
[‡] Università di Pavia.
[§] University of Chicago.
[||] Brown University.
(1) Part 5: D'Accolti, L.; Dinoi, A.; Fusco, C.; Russo, A.; Curci, R. *J. Org. Chem.* **2003**, *68*, 7806–7810.
(2) For examples, see:(a) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI: Greenwich, CT, 1990; Vol 2, Chapter I, pp 1−59. (b) Adam, W.; Zhao, C.-G. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: New York, 2006; Vol. 2, Chapter 14.
(3) (a) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811–22. (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749–6757. (c) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847–2853.

(4) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1–9. See references therein.
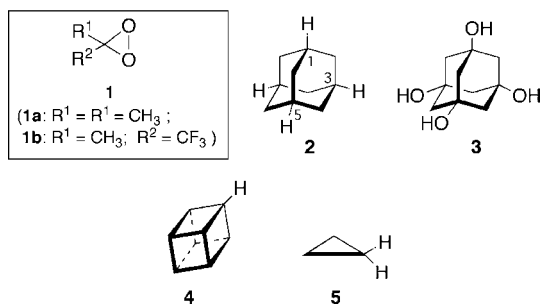(5) D'Accolti, L.; Fusco, C.; Lucchini, V.; Carpenter, G. B.; Curci, R. *J. Org. Chem.* **2001**, *66*, 9063–9066.

Figure 1. Dioxiranes isolated and representative substrates for selective hydroxylations.

We now add the direct dioxirane oxyfunctionalization of cubane (**4**). This is relevant because, after the pioneering work of Eaton and co-workers in the 1960s,[6a] during the past decade cubane chemistry has had a great revival.[6b]

In addition to the theoretical and synthetic challenges inherent to this strained compound, much current interest originates from the unusual stability and compact framework exhibited by cubane functionalized derivatives, making them attractive hyperenergetic materials.[6b] To our knowledge, no effective methods for the *direct* hydroxylation of this substrate have been reported. Classical "electrophilic" oxidants (e.g., MCPBA) are ineffective to this end; also, cubane is found as a poor substrate for methane monooxygenase systems (MMO) or for P-450 enzyme oxidations, requiring extended reaction times to effect hydroxylation in pitifully low yields (ca. 0.05%).[6c]

In the course of investigations herein, we verified that low yield hydroxylation also holds when dimethyldioxirane (**1a**) is applied to cubane (**4**). This can be ascribed to the fact that the exocyclic orbitals in this strained cage compound are highly pyramidalized (C−C−H angle 123−127 ± 2°) and *s* rich.[6a]

We now report on the reactivity of the powerful TFDO (**1b**) toward cubane (**4**) in comparison with a few reference compounds of choice, namely, adamantane (**2**) and cyclopropane (**5**).

We find that treatment of cubane (**4**) in acetone or CH_2Cl_2 with isolated TFDO (**1b**) at subambient temperature gives cubanol (**6**) in excellent yield (98%) (eq 1). In a typical laboratory-scale reaction, cubane could be functionalized in milligram quantities, and 5−10 mg of cubanol (**6**) could be obtained readily within short reaction times.

The structure of isolated **6** could be established spectroscopically. Its IR spectrum showed a strong O−H stretching absorption at 3421 cm^{-1}. In its {^{1}H}^{13}C NMR spectrum, four resonances are apparent: one *C*−OH at 56.0 ppm and three well-resolved methine carbon signals attributed to unfunctionalized cubane carbons, one at 55.7 ppm (α-*C*H) and two

in the high-field region (at 40.9 and 40.0 ppm, respectively). The EI mass spectrum gave M$^+$(21) *m/z* 120.06, and the formula C_8H_8O was confirmed by combustion analysis.
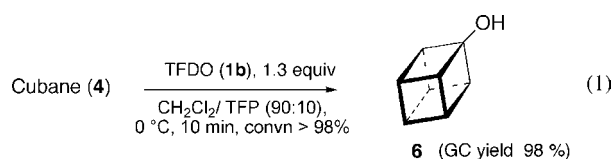
Further oxidation of cubanol **6** with TFDO in acetone (or CH_2Cl_2) solution (eq 2) affords *selectively* the symmetrical
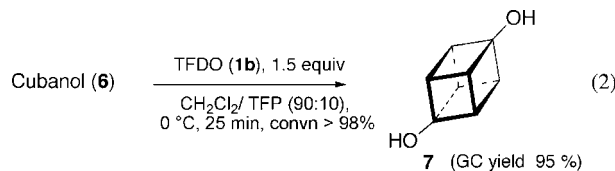
cubane-1,4-diol (**7**) as the only isolable product, and this was identified by physical and spectroscopic data in full agreement with the literature.[7] Structure verification of diol **7** was straightforward given the analytical details[7] and the symmetry evident from the number of carbon signals (two) in the {^{1}H}^{13}C NMR spectrum of the compound.

The ease of the transformations above is remarkable. In view of the known facile access to cubyl cations,[6a] it seems likely that these intermediates are involved as *incipient* species in the oxidation at hand. Actually, experimental evidence, as well as high-level computations, pointed out that—rather than a caged-biradical "rebound" mechanism resembling P-450 oxygenations—a rather concerted "oxenoid" mechanism applies (Figure 2).[4,8] On the whole, the
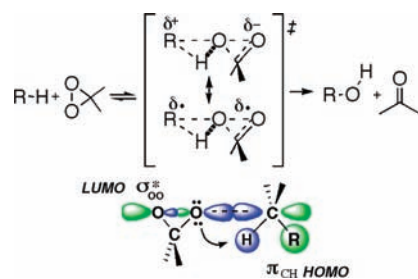

Figure 2. Concerted mechanism and general FMO model for dioxirane O-insertion into alkane C−H bonds.

process sketched in Figure 2 represents a practically *concerted* (albeit nonsynchronous) dioxirane O-insertion into C−H bonds.[4]

The transition state thereof involves a shallow triangular C−H−O assembly as verified through high-level calcula-

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tions,[8−10] including those reported below. These support the view that negative charge is being transferred to the dioxirane from cubane, thus leaving behind partial positive charge distributed over the proximal hydrocarbon C−H centers.

As expected, due to the electron-withdrawing OH group of cubanol (6), further TFDO "electrophilic" hydroxylation to the diol 7 is slower under comparable conditions (eq 2), as verified by the kinetic data reported in Table 1 (entries 2 and 5).

Table 1. Rates of Cubane and of Cubanol Monohydroxylation by TFDO (1b) in Acetone, as Compared to Rates of Adamantane and Cyclopropane

no.	substrate	t (°C) ^{a}	$k_2{}^b$ (M^{-1}·s^{-1})
1	adamantane (2)	− 19	1.80
2	cubane (4)	− 19	0.084
3	"	− 10	0.150
4	"	0	0.300
5	cubanol (6)	− 19	0.035
6	cyclopropane (5)	− 19	< 0.8·10^{-6c}
7	"	0	< 2.8·10^{-6c}

^{a} ± 0.2 °C. ^{b} Unless noted otherwise, kinetic data were obtained by monitoring the decay with time of substrate concentration (calibrated GC). Initial concentrations of the alkane and of TFDO were kept in the range (8 ÷ 4) × 10^{-3} M and rate constants calculated from integrated second-order rate-law plots linear to over 50−80% reaction. The data shown are average values (±8%) from two or more independent runs. ^{c} Second-order constants were estimated as k_1/[cyclopropane]$_o$, with k_1 values (±10%) from experiments run under pseudo-first-order conditions with [cyclopropane]$_o$ in 60-fold excess over [1b]$_o$ (0.04 M); the decrease of TFDO concentration with time was followed spectrophotometrically by monitoring the absorbance at 333 nm; with [5]$_o$ = 2.43 M and [TFDO]$_o$ = 0.04 M, the averaged first-order rate constants were k_1 = 1.9 × 10^{-6} s^{-1} and 6.8 × 10^{-6} s^{-1}, respectively, at −19 and 0 °C.

It seems unlikely, however, that distance from the electron-withdrawing OH group would be sufficient to account for the fact that the further hydroxylation of cubanol (6) to the diol 7 is *exclusively* at C-4. It would be easier to understand had this second hydroxylation occurred instead at C-3; the ab intio 6-31G* calculations (including electron correlation) by Borden and Hrovat[11a] on cubyl cation point to efficient charge delocalization to the C-2 and C-4 positions transmitted via the strained, *p*-rich cubane CC bonds,[11] in agreement with the results of Eaton et al. on the relative rates of solvolysis of C-4 substituted cubyl tosylates.[11b]

On the basis of these computational and experimental results, formation of a positive charge at C-4 of 1-cubanol (6) would be expected to be disfavored. Therefore, the exclusive functionalization of cubanol at C-4 argues against a transition structure in which much carbocationic character is developed at this carbon.

Actually, our initial B3LPY calculations, performed using the parent dioxirane H_2CO_2 in lieu of TFDO as the oxidant, failed to predict exclusive functionalization at C-4 of cubanol (6). Further work is in order to clarify the origin of this peculiar lack of congruence between computations and the experimental result.

In an attempt to find if *s*-character in the tertiary C−H bonds undergoing O-insertion is important, we determined the dioxirane oxidation rate of cubane (4) in comparison with that of two reference substrates, namely, adamantane (2) (purely sp^3 C−H) and cyclopropane (5) (C−H *quasi* sp^2) (Table 1).

Because of the high reactivity of TFDO and of the volatility of most substrates (especially 5), kinetic runs were performed most conveniently at subambient temperatures. The data in Table 1 establish that dioxirane 1b reactivity toward the given substrates is adamantane > cubane ≫ cyclopropane; even correcting for statistical factors, this is in line with the increasing *s* character of the C−H bonds, i.e., respectively, ca. 25, 30, and 33%. Nonetheless, as cubane is more reactive than cyclopropane by a factor of over 10^5, despite similar formal C−H hybridization, something more must be important. Tentatively, one might envisage that this small-ring compound—in reaching a distorted dsp^3 transition state such as that sketched in Figure 2—would face a considerable increase in endocyclic angle strain.

On closer analysis, we found that in fact no appreciable amount of cyclopropanol, nor of ring-open oxidation products, could be detected by GC-MS or NMR after exposure of cyclopropane to TFDO. Indeed, the first-order rate constants measured for TFDO decay *in the absence of cyclopropane* are k_1 = 2.8 × 10^{-6} s^{-1} at −19 °C and 10.7 × 10^{-6} s^{-1} at 0 °C, i.e., practically identical (within ±15%) with the pseudo-first-order rate constants estimated for TFDO decay in the presence of excess cyclopropane (Table 1, note *c*).

As shown in Figure 3 and Table 2, the markedly higher reactivity of cubane over cyclopropane with dioxiranes TFDO (1b) and DDO (1a) is in agreement with ab initio calculations for the gas phase and in solution at 25 °C (cf: entry 1 and 2 with 5 and 6, Table 2).[12]

On the basis of the $\Delta\Delta G_{298}{}^{\ddagger}$ values from data in Table 2, one could estimate a relative rate of cubane/cyclopropane of over 10^{11} at 25 °C in acetone!

In the cyclopropane case, it should be mentioned that the possibility of dioxirane attack at the C−C bond (**TS 3**, Figure 3) can not be discounted a priori. However, inspection of data collected in Table 2 points out that this avenue also continues to be largely disfavored with respect to cubane oxidation (entries 1 and 2).[12]

In line with these results, one should recall that oxidative scission of the cyclopropane ring was never observed when a series of alkyl cyclopropanes[1] or of some polycyclic hydrocarbons encompassing a cyclopropane ring[5] were made to react with the powerful TFDO. It seems that the only

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(10) For a comprehensive review of dioxirane computations, see:Bach, R. D. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: New York, 2006; Vol 2, Chapter 1. See references therein.

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(12) For both TFDO and DDO oxidation, B3LYP/6-311+G(2d,p) data are compared with those at the B3LYP/6-31G(d) level in the Supporting Information.
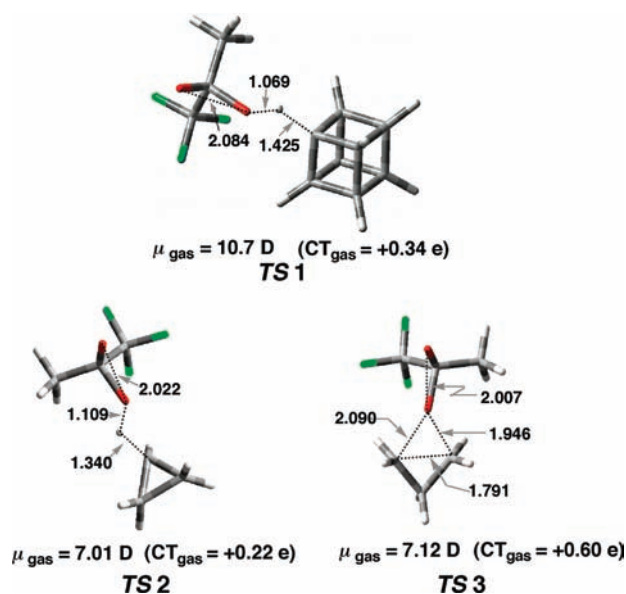
Figure 3. Optimized [B3LYP/6-311+G(2d,p)] transition structures for the oxyfunctionalization of cubane and of cyclopropane with (TFDO). Bond distances in Å; CT = charge transfer.

exception reported so far is the DDO oxidation of the unstable 1,3-didehydroadamantane, which presents a highly strained cyclopropane C−C bond having a distinct biradical character.[13]

The calculations do corroborate the experimental finding that DDO is unsuitable for the oxidation of cubane (Table 2, entries 3 and 4); indeed, the energy barrier opposing the DDO reaction is estimated to be some 13 kcal·mol^{-1} higher than that for TFDO in acetone. The far more powerful TFDO (**1b**) allows one to carry out the oxygenations of cubane efficiently.[4]

As observed in several cases, the hydroxylation of hydrocarbon C−H bonds using DDO can be inconveniently slow, so that the radical decomposition of the oxidant might be triggered.[14,15]

Table 2. Calculated [(B3LYP/6-311+G(2d,p)] Energy Barriers and Activation Parameters (kcal·mol^{-1}) for the Oxyfunctionalization of Cubane and of Cyclopropane with TFDO and with DDO[12]

no.	reaction	phase	$\Delta E^{\ddagger}$	$\Delta H_{298}^{\ddagger}$	$\Delta G_{298}^{\ddagger}$
1	cubane (**4**) + TFDO				
	(**TS1**)	gas	18.91	16.59	22.47
2	”	acetone	11.40	9.08	14.96
3	cubane (**4**) + DDO	gas	29.59	27.55	33.18
4	”	acetone	24.65	22.61	28.24
	cycloprop.(**5**) + TFDO				
5	(**TS2**)	gas	29.82	27.45	33.99
6	”	acetone	26.16	23.79	30.33
7	cycloprop. (**5**) + DDO	gas	37.23	34.95	41.22
8	”	acetone	34.61	32.33	38.60
	cycloprop (**5**) + TFDO				
9	(**TS3**)	gas	30.35	30.67	38.25
10	”	acetone	24.95	25.27	32.85

The *direct* TFDO hydroxylation of cubane in high yield and, if desired, a position-specific second hydroxylation (also high yield as reported here) are especially valuable since the synthesis of cubanol (**6**) and of cubane-1,4-diol (**7**) otherwise requires far more laborious procedures.[7,16]

Supporting Information Available: General experimental procedures and compound characterization data. Sample kinetics runs. Energy, imaginary frequency, Cartesian coordinates, and activation parameters for all *TS*s at the B3LYP/6-311+G(2d,p) level for TFDO and DDO reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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