JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

Enhanced Reactivity in Hydrogen Atom Transfer from Tertiary Sites of Cyclohexanes and Decalins via Strain Release: Equatorial C−H Activation vs Axial C−H Deactivation

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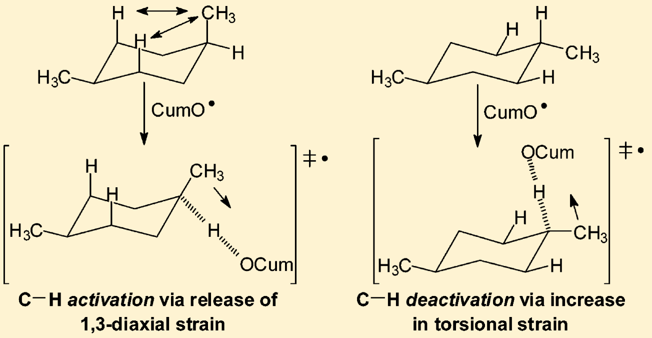
Supporting Information

ABSTRACT: Absolute rate constants for hydrogen atom transfer (HAT) from cycloalkanes and decalins to the cumyloxyl radical (CumO$^\bullet$) were measured by laser flash photolysis. Very similar reactivities were observed for the C−H bonds of cyclopentane and cyclohexane, while the tertiary C−H bond of methylcyclopentane was found to be 6 times more reactive than the tertiary axial C−H bond of methylcyclohexane, pointing toward a certain extent of tertiary axial C−H bond deactivation. Comparison between the *cis* and *trans* isomers of 1,2-dimethylcyclohexane, 1,4-dimethylcyclohexane and decalin provides a quantitative evaluation of the role played by strain release in these reactions. k_H values for HAT from tertiary equatorial C−H bonds were found to be at least 1 order of magnitude higher than those for HAT from the corresponding tertiary axial C−H bonds ($k_{H(eq)}/k_{H(ax)}$ = 10−14). The higher reactivity of tertiary equatorial C−H bonds was explained in terms of 1,3-diaxial strain release in the HAT transition state. Increase in torsional strain in the HAT transition state accounts instead for tertiary axial C−H bond deactivation. The results are compared with those obtained for the corresponding C−H functionalization reactions by dioxiranes and nonheme metal-oxo species indicating that CumO$^\bullet$ can represent a convenient model for the reactivity patterns of these oxidants.



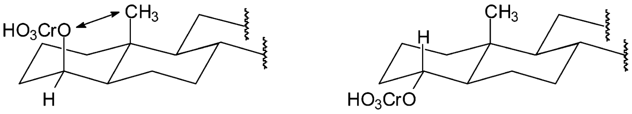
INTRODUCTION

Site-selective functionalization of unactivated aliphatic C−H bonds represents one of the main challenges of modern synthetic organic chemistry.[1−4] These bonds are ubiquitous in organic molecules, and their direct functionalization can offer the opportunity to simplify synthetic routes, avoiding the prefunctionalization of substrates associated with traditional functional group manipulations and interconversions that are widely employed in synthetic procedures. As pointed out recently,[5] in order to plan complex-molecule total syntheses that utilize one or multiple C−H activation steps, a profound understanding of even the subtlest reactivity trends is needed.

The factors that govern site selectivity in C−H functionalization have been discussed in detail,[2−7] providing useful guidelines for the possible accomplishment of this challenging synthetic goal. These include bond strengths, polar effects (also named electronic or inductive effects), conjugation and hyperconjugation, steric and stereoelectronic effects and strain release. The latter effect has gained increasing attention in recent years and is now recognized as an important factor that can be exploited for the selective C−H bond functionalization of cyclic substrates.

Strain release was first proposed by Eschenmoser in 1955 in a study on the chromic acid oxidation of steroidal alcohols.[8] The observation that axial alcohols reacted faster than equatorial alcohols was explained on the basis of a release of 1,3-diaxial strain in the transition state. In the former alcohols, planarization of the carbon undergoing oxidation alleviates the unfavorable 1,3-diaxial interaction between the esterified hydroxyl group and a methyl group leading, as compared to the equatorial alcohols, to a decrease in the activation barrier and to a corresponding increase in reactivity (Scheme 1).

Scheme 1

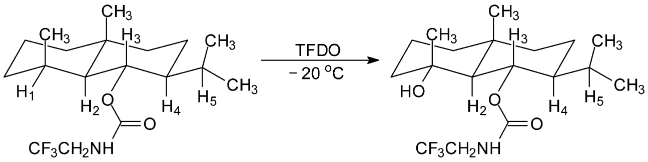


In the framework of site-selective C−H functionalizations, the importance of strain release was recently highlighted by Baran in the selective oxidation of the 2,2,2-trifluoroethyl carbamate of the eudesmane terpene dihydrojunenol[9] and, more recently, of a derivative of the pentacyclic triterpene betulin,[10] by methyl(trifluoromethyl)dioxirane (TFDO). In the former compound, among the five tertiary C−H bonds available selective oxidation of the equatorial C−H$_1$ was observed (Scheme 2).

Received: March 21, 2015
Published: April 7, 2015

DOI: 10.1021/acs.joc.5b00636
J. Org. Chem. 2015, 80, 4710−4715

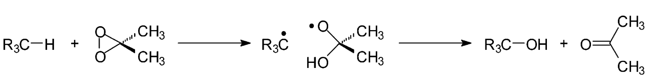
Scheme 2



The explanation in terms of release of 1,3-diaxial strain in the transition state for C−H_1 oxidation was further supported by the observation that in the reactions with TFDO, replacement of the ring-junction axial methyl group by hydrogen led to a 3-fold decrease in reactivity.[5]

The mechanism by which dioxiranes oxidize aliphatic C−H bonds has been strongly debated.[7,11] A recent computational study carried out by Houk on the reactions of dimethyldioxirane (DMDO) with substituted cyclohexanes and *trans*-decalins provides strong support to the important role of strain release in these oxidations, pointing toward a mechanism that proceeds through hydrogen atom transfer (HAT) from a substrate C−H bond to DMDO followed by in cage collapse of the first formed radical pair as described in Scheme 3.[12] An analogous mechanistic picture was obtained for the more reactive oxidant TFDO. This mechanism fully accounts for the site-selectivity and retention of stereochemistry at the oxidized carbon observed in these reactions.

Scheme 3

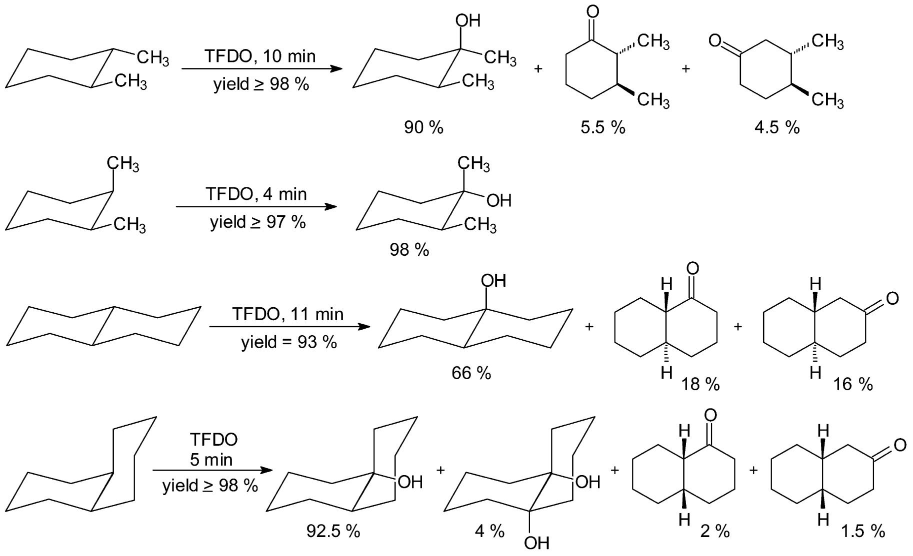


On the basis of this picture and differently from the chromic acid oxidations described above,[8] in the reaction described in Scheme 2 the carbon undergoing oxidation is sp^3 in both the substrate and the product and strain release is now associated with planarization of an incipient carbon radical in the transition state for HAT. Some relevant examples of the selectivities observed in the C−H oxidation by TFDO of cyclic and bicyclic hydrocarbon substrate couples that have often been taken as mechanistic probes for the study of the reactivity and selectivity patterns observed in these reactions, such as *cis*- and *trans*-1,2-dimethylcyclohexane, and *cis*- and *trans*-decalin are displayed in Scheme 4.[13] In all the examples shown, tertiary equatorial C−H bonds display a significantly higher reactivity than the corresponding tertiary axial C−H bonds and, as a consequence, competitive oxidation of secondary sites is significantly less important for the substrates that bear tertiary equatorial C−H bonds.

Similar reactivity and selectivity patterns were also observed in aliphatic C−H oxidations catalyzed by nonheme iron complexes employing H_2O_2 as terminal oxidant. Comparison between substrate couples such as *cis*- and *trans*-1,2-dimethylcyclohexane, *cis*- and *trans*-decalin, and *cis*- and *trans*-4-methylcyclohexylpivalate, showed in all cases a significantly higher reactivity for tertiary equatorial C−H bonds as compared to the corresponding tertiary axial C−H bonds.[14−16] Most importantly, these reactions appear to share mechanistic features with aliphatic C−H oxidations by dioxiranes,[12] as the reactions catalyzed by nonheme iron complexes have also been shown to occur with retention of configuration at the oxidized tertiary carbon center and have been generally described on the basis of a mechanism that proceeds through HAT from a substrate C−H bond to an iron-oxo species followed by rapid oxygen rebound.[14d,16−18] On the basis of this mechanistic picture, also with these catalysts homolytic C−H bond cleavage will be accompanied by a certain extent of planarization of an incipient carbon radical in the transition state, accounting, in the reactions of cyclohexane and decalin derivatives, for the higher reactivity of tertiary equatorial C−H bonds as compared to tertiary axial C−H bonds via release of 1,3-diaxial strain.

In all the studies described above, information on the C−H bond reactivities and on the associated selectivities were obtained through product studies. Quite surprisingly, limited kinetic information on these effects is available and mostly refers to the oxidation of cyclohexanols by chromic acid,[8,19] whereas, to the best of our knowledge, no direct kinetic study on the HAT reactivity of tertiary C−H bonds of cyclic and bicyclic hydrocarbons is presently available. This information would be of great importance because it can provide a quantitative evaluation of the role of strain release on these

Scheme 4



reactions. In view of the description of the initial step of aliphatic C−H oxidations by dioxiranes and iron-oxo species as a HAT reaction, we felt that a genuine HAT reagent such as the cumyloxyl radical ($PhC(CH_3)_2O^\bullet$, CumO$^\bullet$) could offer the unique opportunity to probe this issue. As mentioned previously,[20] CumO$^\bullet$ can be easily generated in a variety of organic solvents by UV photolysis of commercially available dicumyl peroxide and, most importantly, is characterized by a visible absorption band and a lifetime that allow the direct measurement of HAT rate constants by ns laser flash photolysis (LFP). Along these lines, in order to obtain information on the HAT reactivity of equatorial and axial tertiary C−H bonds, aimed at a quantitative evaluation of the importance of strain release in C−H oxidations, we have carried out a detailed time-resolved kinetic study on the reactions of CumO$^\bullet$ with a variety of cyclic and bicyclic hydrocarbons, namely: cyclopentane, methylcyclopentane, cyclohexane, methylcyclohexane, *tert*-butylcyclohexane, 1,1-dimethylcyclohexane, *cis*-1,2-dimethylcyclohexane, *trans*-1,2-dimethylcyclohexane, *cis*-1,4-dimethylcyclohexane, *trans*-1,4-dimethylcyclohexane, *cis*-decalin and *trans*-decalin.

RESULTS

CumO$^\bullet$ was generated by 355 nm laser flash photolysis (LFP) of argon-saturated acetonitrile solutions (T = 25 °C) containing 1.0 M dicumyl peroxide. In this solvent CumO$^\bullet$ displays an absorption band in the visible region of the spectrum centered at 485 nm,[21,22] and mainly decays through cleavage of the C−CH_3 bond.[20,22,23]

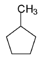
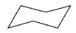
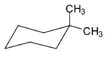
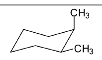
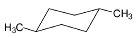
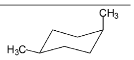
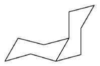
The time-resolved kinetic studies were carried out by LFP following the decay of the CumO$^\bullet$ visible band as a function of the concentration of added substrate. For all the substrates studied excellent linear relationships were obtained when the observed rate constants (k_{obs}) were plotted against concentration of added substrate and the second-order rate constants for HAT to CumO$^\bullet$ (k_H) were obtained from the slopes of these plots. The pertinent k_{obs} vs [substrate] plots are displayed in the Supporting Information (SI, Figures S1−S11). The k_H values thus obtained for the reactions of CumO$^\bullet$ with the cycloalkanes and decalins are collected in Table 1. Also included in this table is the k_H value measured previously for reaction of CumO$^\bullet$ with cyclohexane in acetonitrile solution.[24]

DISCUSSION

The k_H values measured for cyclopentane and cyclohexane (k_H = 9.54×10^5 and 1.1×10^6 M^{-1} s^{-1}, respectively), when normalized for the number of hydrogen atoms (10 and 12, respectively), clearly indicate that on a per-hydrogen basis the C−H bonds of these substrates display a very similar reactivity toward CumO$^\bullet$ (9.5×10^4 and 9.2×10^4 M^{-1} s^{-1}, respectively). This observation points toward the absence of significant differences in HAT reactivity between the axial and equatorial C−H bonds of cyclohexane, in line with recent computational studies by Houk.[12] On going from cycloalkanes to the corresponding methylcycloalkanes, an increase in k_H is observed for methylcyclopentane (k_H = 1.31×10^6 M^{-1} s^{-1}), while a slight decrease in k_H is observed for methylcyclohexane (k_H = 1.01×10^6 M^{-1} s^{-1}).[25] By reasonably assuming that the methylene groups of both the cycloalkanes and methylcycloalkanes are characterized by the same reactivity toward CumO$^\bullet$,[26] and by taking into account that methylcyclohexane mostly exists in a conformation where the methyl group occupies an equatorial position,[27] comparison between these values shows that in methylcyclopentane the tertiary C−H bond is about 6 times more reactive than a secondary C−H bond (k_H(*tert*)/k_H(*sec*) ~ 6), in line with the reactivity trends that have been generally observed in HAT reactions from aliphatic C−H bonds to tertiary alkoxyl radicals.[28] On the other hand, quite surprisingly, in methylcyclohexane the tertiary axial C−H bond and the secondary C−H bonds display very similar reactivities (k_H(*tert*)/k_H(*sec*) ~ 1). In other words, in HAT reactions to CumO$^\bullet$, the tertiary C−H bond of methylcyclopentane is about 6 times more reactive than the tertiary axial C−H bond of cyclohexane. We will return on this difference in reactivity later on.

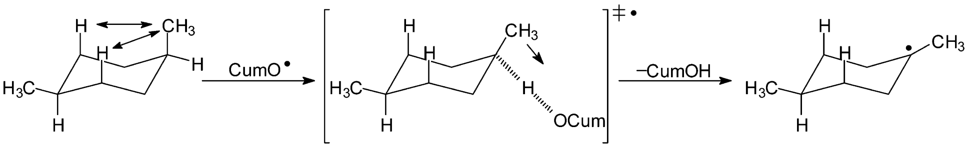
Within the cyclohexane series, a decrease in k_H was measured on going from cyclohexane and methylcyclohexane to *tert*-butylcyclohexane and 1,1-dimethylcyclohexane, for which k_H = 8.2×10^5 and 7.7×10^5 M^{-1} s^{-1}, respectively. This behavior can be explained on the basis of the deactivation toward HAT of the tertiary axial C−H bond of *tert*-butylcyclohexane and of the proximal methylene groups at C2 and C6 of both substrates, determined by steric and stereoelectronic effects, as pointed out in previous studies on the oxidation of the same substrates catalyzed by nonheme iron complexes,[14b,c,15] and in the oxidation of 1,1-dimethylcyclohexane with TFDO.[5] The reaction of *tert*-butylcyclohexane catalyzed by the [Fe(*S*,*S*-PDP)] complex in the presence of H_2O_2 led to the formation of oxidation products at C2, C3 and C4 in a 2:59:12 ratio. 1-*tert*-Butylcyclohexanol was not observed among the reaction products, indicating that C1 is not oxidized under these conditions (see later).[15] The reactions of 1,1-dimethylcyclohexane catalyzed by [Fe(*S*,*S*-PDP)],[15] [Fe(TfO)$_2$(^{Me,Me}Pytacn)],[14b] and by a series of highly structured nonheme iron complexes,[14c] in the presence of H_2O_2, led in all cases to the formation of the oxidation product at the sterically more demanding site (C2) in a lower statistical yield as compared to the C3 and C4 sites. Along this line, oxidation of 1,1-dimethylcyclohexane by TFDO led to the formation of oxidation products at C3 and C4 in a statistical 2:1 ratio, indicating that with this substrate strain release, via oxidation of

Table 1. Second-Order Rate Constants for Reaction of the Cumyloxyl Radical (CumO$^\bullet$) with Cycloalkanes, Alkylcycloalkanes, Dimethylcyclohexanes and Decalins[a]

k_H / M^{-1} s^{-1}	 $9.54 \pm 0.08 \times 10^5$	 $1.31 \pm 0.02 \times 10^6$	 $1.1 \pm 0.1 \times 10^6$ [b]	 $1.01 \pm 0.05 \times 10^6$
k_H / M^{-1} s^{-1}	 $8.2 \pm 0.3 \times 10^5$		 $7.7 \pm 0.1 \times 10^5$	
k_H / M^{-1} s^{-1}	 $1.03 \pm 0.02 \times 10^6$	 $2.34 \pm 0.05 \times 10^6$	 $1.10 \pm 0.02 \times 10^6$	 $2.05 \pm 0.06 \times 10^6$
k_H / M^{-1} s^{-1}	 $1.58 \pm 0.05 \times 10^6$		 $2.85 \pm 0.08 \times 10^6$	

[a] Argon-saturated acetonitrile solution, T = 25 °C, 355 nm LFP, [dicumyl peroxide] = 1.0 M. The k_H values have been determined from the slope of the k_{obs} vs [substrate] plots, where the k_{obs} values have been measured following the decay of the CumO$^\bullet$ visible absorption band at 490 nm. Average of at least two determinations. [b] Ref 24.

Scheme 5



the equatorial C−H at C3, plays a negligible role in the activation of methylene C−H bonds.[5]

Moving to the dimethylcyclohexanes, the rate constants collected in Table 1 show that the two *trans* isomers, each characterized by the presence of two tertiary axial C−H bonds, display k_H values ($k_H = 1.03 \times 10^6$ and 1.10×10^6 M^{-1} s^{-1}, for *trans*-1,2-dimethylcyclohexane and *trans*-1,4-dimethylcyclohexane, respectively) that are very similar to those measured for the corresponding reactions of cyclohexane and methylcyclohexane, confirming that in these substrates tertiary axial C−H bonds and secondary C−H bonds display similar reactivities. On the other hand, an approximately 2-fold increase in k_H was observed on going from *trans*-1,2-dimethylcyclohexane and *trans*-1,4-dimethylcyclohexane to the corresponding *cis* isomers ($k_H = 2.34 \times 10^6$ and 2.05×10^6 M^{-1} s^{-1}, for *cis*-1,2-dimethylcyclohexane and *cis*-1,4-dimethylcyclohexane, respectively). By assuming, on the basis of the discussion outlined above, a rate constant for HAT from a tertiary axial C−H bond of methyl- and dimethylcyclohexanes to CumO$^\bullet$ $k_{H(ax)} = 0.9$–1.1×10^5 M^{-1} s^{-1}, comparison between the k_H values measured for the *cis*- and *trans*-dimethylcyclohexanes provides rate constants for HAT from the tertiary equatorial C−H bonds of *cis*-1,2-dimethylcyclohexane and *cis*-1,4-dimethylcyclohexane, $k_{H(eq)} = 1.4 \times 10^6$ and 1.1×10^6 M^{-1} s^{-1}, respectively.[29] On the basis of these values it appears that in the reactions of CumO$^\bullet$ with dimethylcyclohexanes, the reactivity of tertiary equatorial C−H bonds is at least 1 order of magnitude higher than that of tertiary axial C−H bonds ($k_{H(eq)}/k_{H(ax)} = 14$ and 10 for the 1,2- and 1,4-dimethylcyclohexane couples, respectively), thus providing a quantitative evaluation of the role played by strain release in these reactions. The higher reactivity of tertiary equatorial C−H bonds can be accounted for on the basis of the release of 1,3-diaxial strain resulting from planarization of an incipient carbon radical in the transition state for HAT (Scheme 5, showing HAT from *cis*-1,4-dimethylcyclohexane to CumO$^\bullet$).

An analogous behavior was observed for the two isomeric decalins in their reactions with CumO$^\bullet$ ($k_H = 2.85 \times 10^6$ and 1.58×10^6 M^{-1} s^{-1}, for *cis*-decalin and *trans*-decalin, respectively). The difference in k_H between *cis*-decalin and *trans*-decalin is essentially identical to the corresponding difference between *cis*-1,2-dimethylcyclohexane and *trans*-1,2-dimethylcyclohexane, indicating that in these reactions the reactivity of the tertiary equatorial C−H bond in *cis*-decalin is 14 times higher than that of a tertiary axial C−H bond ($k_{H(eq)}/k_{H(ax)} = 14$).

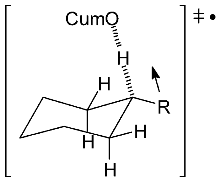
These results are in line with those obtained previously in the oxidation of *cis*-1,2-dimethylcyclohexane, *trans*-1,2-dimethylcyclohexane, *cis*-decalin and *trans*-decalin by TFDO[13] and nonheme iron-oxo species,[14a−c,15] where, as mentioned above, preferential oxidation of tertiary equatorial C−H bonds over tertiary axial C−H bonds was observed in all cases, with competitive oxidation of secondary sites that was significantly more important for the *trans* isomer as compared to the *cis* isomer.

Very importantly, the differences in reactivity observed in the reactions of the two dimethylcyclohexane couples with CumO$^\bullet$ are in agreement with the computed differences in activation energy for the reactions of DMDO with *cis*-1,4- and *trans*-1,4-dimethylcyclohexanes ($\Delta E^\ddagger = 0.7$ kcal mol^{-1}) and with *cis*-1,2- and *trans*-1,2-dimethylcyclohexanes ($\Delta E^\ddagger = 1.1$ kcal mol^{-1}),[12] supporting the hypothesis that HAT from tertiary C−H bonds to CumO$^\bullet$ represents a convenient model for the corresponding oxidations by dioxiranes, where, as mentioned previously, the initial step has been described as a HAT reaction from a substrate C−H bond to a dioxirane oxygen atom (Scheme 3).[12,30]

Taken together, these results clearly show that release of 1,3-diaxial strain plays an important role in the activation of tertiary equatorial C−H bonds in cyclohexanes and decalins. It is however important to point out that the magnitude of the $k_{H(eq)}/k_{H(ax)}$ ratios measured in the reactions of CumO$^\bullet$ with these substrates reflects, in addition to this activation, a certain extent of deactivation of the tertiary axial C−H bonds. This is evidenced by the above-mentioned ∼6-fold decrease in k_H measured on going from methylcyclopentane to methylcyclohexane for HAT from the tertiary C−H bonds and by the observation that whereas in the reactions of *cis*-1,2-dimethylcyclohexane and *cis*-decalin with a number of nonheme iron-oxo species the amount of equatorial tertiary alcohol always exceeded the amount of ketones formed following oxidation at secondary positions, in the corresponding reactions of the *trans* isomers product distributions for oxidation at tertiary (alcohol) and secondary (ketones) positions were generally very close or, in the case of *trans*-decalin, lower than those expected on a statistical basis (1:4 and 1:8, respectively).[14a−c] The latter observation indicates that in addition to CumO$^\bullet$ also nonheme iron-oxo species display comparable reactivities toward the tertiary axial C−H bonds and secondary C−H bonds of these *trans* isomers, suggesting in the same time that, at least in the reactions with these cyclic and bicyclic hydrocarbons, HAT reactions to CumO$^\bullet$ can represent a convenient model for the reactivity of these species.

Along these lines, tertiary axial C−H bond deactivation can be explained in terms of an increase in torsional strain in the HAT transition state (Scheme 6, showing the transition state for HAT from the tertiary axial C−H bond of a generic alkylcyclohexane to CumO$^\bullet$), where planarization of the incipient carbon radical forces the R group toward an unfavorable eclipsed interaction with the equatorial groups on the adjacent positions.

Scheme 6



On the basis of this picture, the energetic barrier for HAT is expected to increase with increasing steric bulk of the R group, strongly influencing axial C−H bond deactivation at tertiary sites. This hypothesis is in full agreement with the selectivity pattern observed in the reaction of *tert*-butylcyclohexane catalyzed by [Fe(*S*,*S*-PDP)] in the presence of H_2O_2 where, as mentioned above, no product deriving from oxidation at the tertiary axial C−H bond was detected,[15] in contrast to the oxidations of *trans*-1,2-dimethylcyclohexane and *trans*-decalin carried out under analogous conditions where sizable amounts of the tertiary axial alcohol were always formed.[14a−c,15]

Along these lines, the selectivity observed by Baran in the oxidation of the 2,2,2-trifluoroethyl carbamate of dihydrojunenol by TFDO (Scheme 2),[9] can be conveniently explained on the basis of the combination of these effects via release of 1,3-diaxal strain associated with C−H_1 oxidation and deactivation of the tertiary axial C−H_2, C−H_3 and C−H_4 bonds.

The selective formation of products at the secondary C2, C3 and C4 positions in the oxidation of *tert*-butylcyclohexane,[15] and the comparable reactivities displayed by CumO$^\bullet$ and nonheme iron-oxo species toward tertiary axial C−H bonds and secondary C−H bonds of cyclohexanes and decalins,[14a−c] clearly indicate that this deactivation effect is sufficient to override the thermodynamic preference for HAT from a tertiary C−H bond.[28]

CONCLUSIONS

By means of time-resolved kinetic studies a quantitative evaluation of the role of strain release on HAT from the tertiary C−H bonds of cycloalkanes to CumO$^\bullet$ has been obtained. The significantly higher k_H values measured for HAT from the tertiary equatorial C−H bonds of cyclohexanes and decalins as compared to the corresponding tertiary axial C−H bonds ($k_{H(eq)}/k_{H(ax)}$ = 10−14), indicates that these bonds are activated toward HAT, pointing in the same time toward a certain extent of tertiary axial C−H bond deactivation. The latter hypothesis is supported by the 6-fold increase in reactivity for the tertiary C−H bond of methylcyclopentane as compared to methylcyclohexane, the similar reactivity observed for the secondary and tertiary axial C−H bonds of methylcyclohexane and by the decrease in k_H measured on going from methylcyclohexane to *tert*-butylcyclohexane. Tertiary equatorial C−H bond activation has been explained on the basis of the previously proposed release of 1,3-diaxial strain in the HAT transition state. On the other hand, tertiary axial C−H bond deactivation reflects an increase in torsional strain in the HAT transition state determined by planarization of an incipient carbon centered radical. These results are in agreement with those obtained previously for C−H functionalization of the same substrates by dioxiranes and nonheme iron-oxo species, supporting the hypothesis that these reactions proceed through a common HAT mechanism and indicating that CumO$^\bullet$ can represent a convenient mechanistic probe for the reactivity patterns of these oxidants in their reactions with aliphatic C−H bonds. In the framework of site-selective C−H functionalization of cyclohexane derivatives, these results indicate that by varying steric bulk of a substituent at a tertiary site these effects can be employed in a complementary fashion for the activation/deactivation of tertiary equatorial/axial C−H bonds, providing a useful tool for the accomplishment of this challenging synthetic goal.

EXPERIMENTAL SECTION

Materials. Spectroscopic grade acetonitrile was used as solvent in the time-resolved kinetic experiments. Cyclopentane, methylcyclopentane, cyclohexane, methylcyclohexane, *tert*-butylcyclohexane, 1,1-dimethylcyclohexane, *cis*-1,2-dimethylcyclohexane, *trans*-1,2-dimethylcyclohexane, *cis*-1,4-dimethylcyclohexane, *trans*-1,4-dimethylcyclohexane, *cis*-decalin and *trans*-decalin were of the highest commercial quality available and were used as received. The purity of the substrates was checked by GC prior to the kinetic experiments and was in all cases >99%. Dicumyl peroxide was of the highest commercial quality available and was used as received.

Laser Flash Photolysis Studies. LFP experiments were carried out with a laser kinetic spectrometer using the third harmonic (355 nm) of a Q-switched Nd:YAG laser, delivering 8 ns pulses. The laser energy was adjusted to ≤10 mJ/pulse by the use of the appropriate filter. A 3.5 mL Suprasil quartz cell (10 mm × 10 mm) was used in all experiments. Argon saturated acetonitrile or isooctane solutions of dicumyl peroxide (1.0 M) were employed. All the experiments were carried out at $T = 25 \pm 0.5$ °C under magnetic stirring. The observed rate constants (k_{obs}) were obtained by averaging 2−5 individual values and were reproducible to within 5%.

Second order rate constant for the reactions of the cumyloxyl radical with the different substrates were obtained from the slopes of the k_{obs} (measured following the decay of the cumyloxyl radical visible absorption band at 490 nm) vs [substrate] plots. Fresh solutions were used for every substrate concentration. Correlation coefficients were in all cases >0.99. The rate constants displayed in Table 1 are the average of at least two independent experiments, typical errors being ≤5%.

ASSOCIATED CONTENT

Supporting Information

Plots of k_{obs} vs [substrate] for the reactions of CumO$^\bullet$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) Project 2010PFLRJR (PRIN 2010-2011) is gratefully acknowledged. We thank Prof. Miquel Costas for helpful discussions and, together with Dr. Mercè Canta, for inspiring this work, and Prof. Lorenzo Stella for the use of a LFP equipment.

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(25) At this stage, it is worth mentioning that because of the multitude of C−H bonds in these substrates, relatively small changes in the measured rate constant can translate into significant changes in selectivity, as clearly shown by the comparison between the k_{H} values measured for reaction of CumO$^{\bullet}$ with methylcyclopentane and methylcyclohexane.

(26) As correctly pointed out by a reviewer, it is implicit from this assumption that there are no significant steric effects for HAT from secondary sites determined by methyl groups at tertiary sites. In view of this assumption, the reactivity ratio given for HAT from the tertiary and secondary C−H bonds of methylcyclopentane should be taken as a lower limit because, if steric effects do play a minor role, at least for HAT from secondary sites that are adjacent to tertiary sites, this will result in a increase in the relative importance of HAT from the tertiary C−H bond.

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(29) By assuming that the $k_{\mathrm{H(ax)}}$ values correspond to one tenth of the k_{H} values measured for HAT from *trans*-1,2-dimethylcyclohexane and *trans*-1,4-dimethylcyclohexane to CumO$^{\bullet}$ ($k_{\mathrm{H}(\mathit{trans}\text{-}1,2)}$ and $k_{\mathrm{H}(\mathit{trans}\text{-}1,4)}$, respectively), and, to a first approximation, that HAT from the other C−H bonds of the substrate couple under consideration is not affected by the equatorial or axial position of the methyl group, $k_{\mathrm{H(eq)}}$ for a given *cis*-dimethylcyclohexane can be obtained from the difference between the k_{H} value measured for HAT from that *cis*-dimethylcyclohexane ($k_{\mathrm{H}(\mathit{cis}\text{-}1,2)}$ or $k_{\mathrm{H}(\mathit{cis}\text{-}1,4)}$) and the difference between k_{H} and $k_{\mathrm{H(ax)}}$ for the corresponding *trans*-dimethylcyclohexane. For example, for *cis*-1,2-dimethylcyclohexane: $k_{\mathrm{H(eq)}} = k_{\mathrm{H}(\mathit{cis}\text{-}1,2)} - (k_{\mathrm{H}(\mathit{trans}\text{-}1,2)} - k_{\mathrm{H(ax)}}) = 2.34 \times 10^{6} - (1.03 \times 10^{6} - 1.0 \times 10^{5}) = 1.4 \times 10^{6}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$.

(30) In this framework, it is important to point out that in the reactions with proline, leucine and valine derivatives, CumO$^{\bullet}$ and DMDO have been shown to display analogous selectivity patterns towards side-chain secondary and tertiary C−H bonds.[31]

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