JOC Article

# Photolysis of 1-Alkylcycloalkanols in the Presence of (Diacetoxyiodo)benzene and $I_2$. Intramolecular Selectivity in the $\beta$-Scission Reactions of the Intermediate 1-Alkylcycloalkoxyl Radicals

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The C−C $\beta$-scission reactions of 1-alkylcycloalkoxyl radicals, generated photochemically by visible light irradiation of $CH_2Cl_2$ solutions containing the parent 1-alkylcycloalkanols, (diacetoxy)-iodobenzene (DIB), and $I_2$, have been investigated through the analysis of the reaction products. The 1-alkylcycloalkoxyl radicals undergo competition between ring opening and C-alkyl bond cleavage as a function of ring size and of the nature of the alkyl substituent. With the 1-propylcycloheptoxyl, 1-propylcyclooctoxyl ,and 1-phenylcyclooctoxyl radicals, formation of products deriving from an intramolecular 1,5-hydrogen atom abstraction reaction from the cycloalkane ring has also been observed. The results are discussed in terms of release of ring strain associated to ring opening, stability of the alkyl radical formed by C-alkyl cleavage, and with cycloheptoxyl and cyclooctoxyl radicals, also in terms of the possibility of achieving a favorable geometry for intramolecular hydrogen atom abstraction.

Alkoxyl radicals are important intermediates which play a major role in the photooxidation of hydrocarbons in the atmosphere[2] and in several processes occurring in biological systems.[3] Moreover, following the increasing importance experienced in recent years by radicals in organic synthesis, alkoxyl radical chemistry has been successfully exploited in synthetically useful processes, mainly through cyclization,[4] $\beta$-fragmentation,[5] and 1,5 hydrogen atom transfer reactions.[6] Among these processes, C−C $\beta$-scission leading to a carbonyl compound and an alkyl radical is one of the most important reactions of alkoxyl radicals (Scheme 1).

With tertiary alkoxyl radicals bearing different alkyl groups it is possible, at least in principle, to obtain three different C−C bond fragmentations and accordingly the intramolecular selectivity in the $\beta$-scission reactions of tertiary alkoxyl radicals has been the subject of detailed investigation.[7−13] The main conclusion of these studies was that cleavage generally leads to the most stable possible alkyl radical. However, when considering the ring-opening reactions of cycloalkoxyl radicals it was suggested that other factors may play a role. For example, it was found that ring opening of the cyclopentoxyl radical is more than 100 times faster than ethyl radical ejection from the 2-butoxyl radical.[14] A similar behavior was observed when the ring opening of the 1-methylcyclopentoxyl radical was compared with ethyl radical

(1) (a) Università "Tor Vergata". (b) Università "La Sapienza".

(2) See, for example: Orlando, J. J.; Tyndall, G. S.; Wallington, T. J. *Chem. Rev.* **2003**, *103*, 4657−4689. Atkinson, R. *Int. J. Chem. Kinet.* **1997**, *29*, 99−111.

(3) See, for example: Davies, M. J.; Headlam, H. A. *Free Rad. Biol. Med.* **2002**, *32*, 1171−1184. Halliwell, B.; Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*, 3rd ed.; Oxford University Press: New York, 1999. Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 2253−2297. Ullrich, V.; Brugger, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1911−1919.

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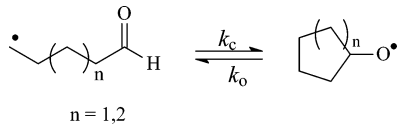
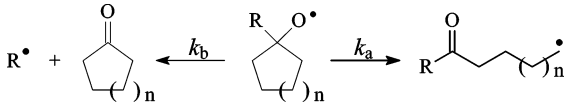
**SCHEME 1**

**SCHEME 2**



n = 1,2

**SCHEME 3**



| | | |
|---|---|---|
| n = 1 | R = $CH(CH_3)_2$ | $k_a/k_b$ = 14 |
| n = 2 | R = $CH_2CH_3$ | $k_a/k_b$ = 7 |
| n = 2 | R = $CH(CH_3)_2$ | $k_a/k_b$ = 0.1 |

ejection from the 2-methyl-2-butoxyl radical.[10b] Results which were rationalized in terms of the relief of ring strain associated to cyclopentane ring opening.

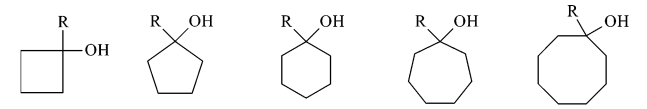
For what concerns instead the comparison between ring-opening reactions of cycloalkoxyl radicals having different ring size, Beckwith studied the reversibility of the *exo* cyclization reaction of *ω*-formyl alkyl radicals by means of competitive kinetics (Scheme 2).[15]

Rate constants for *β*-scission (ring-opening) of the cyclopentoxyl and cyclohexoxyl radicals were determined as $k_o = 4.7 \times 10^8$ and $1.1 \times 10^7$ $s^{-1}$, respectively, in line with the greater ring strain associated with a five-membered ring as compared to a six-membered one.[16] In agreement with this conclusion are also the results of relative reactivity studies showing that the 1-methylcyclopentoxyl radical undergoes ring-opening 10 times faster than the 1-methylcyclohexoxyl one.[10b] Along this line, in a study of the intramolecular selectivity in the C−C *β*-scission reactions of 1-isopropylcyclopentoxyl and 1-R-cyclohexoxyl radicals (R = Et, $^i$Pr) it was shown that in the former radical ring opening is the major fragmentation pathway, whereas in the 1-R-cyclohexoxyl radicals ring opening is the major fragmentation pathway when R = Et while C−R cleavage predominantes when R = $^i$Pr (Scheme 3).[12]

Thus, variations in both ring size and nature of the alkyl ring substituent R may influence the competition between ring opening and C−R cleavage in the 1-alkylcycloalkoxyl radical.

In view of the importance of cycloalkoxyl radical ring-opening reactions in organic synthesis,[5,17,18] of the limited amount of data available on the intramolecular selectivity in C−C *β*-scission reactions of 1-alkylcycloalkoxyl radicals, and in order to provide additional information on the factors governing this selectivity, we have carried out a systematic product study for the *β*-scission reactions of an extended series of 1-alkylcycloalkoxyl radicals,

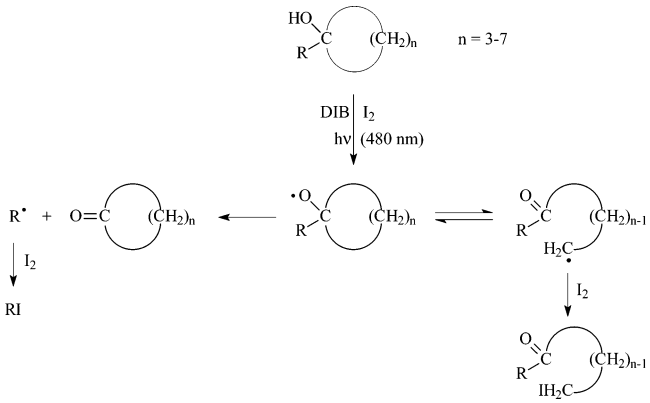
**CHART 1**



**1f:** R = allyl
**1g:** R = benzyl

| | | | | |
|---|---|---|---|---|
| **2a:** R = Me | **3a:** R = Me | **4c:** R = Pr | **5c:** R = Pr |
| **2b:** R = Et | **3b:** R = Et | **4d:** R = *i*Pr | **5d:** R = *i*Pr |
| **2c:** R = Pr | **3c:** R = Pr | **4e:** R = *t*Bu | **5e:** R = *t*Bu |
| **2d:** R = *i*Pr | **3d:** R = *i*Pr | **4g:** R = benzyl | **5g:** R = benzyl |
| **2e:** R = *t*Bu | **3e:** R = *t*Bu | **4h:** R = Ph | **5h:** R = Ph |
| **2f:** R = allyl | **3g:** R = benzyl | | |
| **2g:** R = benzyl | **3h:** R = Ph | | |
| **2h:** R = Ph | **3i:** R = neopentyl | | |
| **2i:** R = neopentyl | | | |

**SCHEME 4**



where both ring size and nature of the alkyl group have been varied. The alkoxyl radicals have been generated photochemically by visible light irradiation of $CH_2Cl_2$ solutions containing the parent 1-alkylcycloalkanols (Chart 1), (diacetoxy)iodobenzene (DIB), and $I_2$ (Suarez's reagent).

The DIB/$I_2$ reagent is a well-known reagent based on a hypervalent iodine compound (DIB) which, in the presence of visible light, is able to convert hydroxyl-containing substrates into products deriving from intermediate oxygen-centered radicals.[5a,17] The main advantage of this reagent is represented by the fact that the alkoxyl radicals can be easily generated from the parent alcohols. Moreover, irradiation with visible light prevents the occurrence of undesired photochemical reactions of the carbonyl products formed by alkoxyl radical *β*-scission, which can instead occur when UV light is used for alkoxyl radical generation.[19]

A mechanism for alkoxyl radical formation, proceeding through the photochemical decomposition of an intermediate hypoiodite, which is generated by thermal reaction of DIB, $I_2$, and the alcohol, has been recently proposed.[20]

With 1-alkylcycloalkanols, the overall process can be described to occur according to Scheme 4, where an intermediate 1-alkylcycloalkoxyl radical is initially formed by visible light irradiation of 1-alkylcycloalkanol/DIB/$I_2$ mixtures and then undergoes competition between ring opening and C−R cleavage as a function of ring size and nature of the R group. The carbon-centered radicals formed by alkoxyl radical *β*-scission are efficiently trapped

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**TABLE 1. Product Distributions Observed after Irradiation of Ar-Saturated $CH_2Cl_2$ Solutions ($T$ = 20 °C) Containing 1-Alkylcyclobutanols (1f,g), DIB, and $I_2$[a]**

| Substrate | Products | Conversion (%) | Q[b] |
|---|---|---|---|
| **1f** (R = $CH_2CH{=}CH_2$) | $H_2C{=}CHCH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2I$ | 44[c] | < 0.01[d] |
| **1g** (R = $CH_2C_6H_5$) | $C_6H_5CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2I$ | 62[e] | < 0.01[d] |

[a] [substrate] = 10 mM; [DIB] = 11 mM; [$I_2$] = 10 mM; $\lambda_{irr}$ = 480 nm. [b] Ratio between C−R cleavage and ring-opening products. [c] Irradiation time = 1 min. [d] No C−R cleavage products detected. [e] Irradiation time = 2 min.

by iodine,[21−23] minimizing the competition with side reactions which may influence product distribution.

## Results

Argon-saturated $CH_2Cl_2$ solutions containing the 1-alkylcycloalkanol (**1**−**5**) (10 mM), DIB (11 mM), and $I_2$ (10 mM) were irradiated with visible light ($\lambda_{max} \approx$ 480 nm) at $T$ = 20 °C. The irradiation time was chosen in such a way as to avoid complete substrate conversion. After workup of the reaction mixture, the reaction products were generally identified by GC−MS and $^1$H NMR and quantitatively determined, together with the unreacted substrate by GC and $^1$H NMR, using bibenzyl as internal standard.

The reaction products are reported, together with substrate conversion and ratio between C−R cleavage and ring-opening products (**Q**), in Tables 1−5 for 1-alkylcyclobutanols (**1f**,**g**), 1-alkylcyclopentanols (**2a**−**i**), 1-alkylcyclohexanols (**3a**−**e**,**g**−**i**), 1-alkylcycloheptanols (**4c**−**e**,**g**,**h**) and 1-alkylcyclooctanols (**5c**−**e**,**g**,**h**), respectively.

The results collected in Table 1 for 1-allylcyclobutanol (**1f**) and 1-benzylcyclobutanol (**1g**) show the formation of the corresponding ring-opened iodoketone (7-iodo-1-hepten-4-one and 5-iodo-1-phenylpentan-2-one, respectively) as the exclusive reaction product.

The results obtained for the 1-alkylcyclopentanol series (Table 2) show the exclusive formation of the corresponding ring-opened iodoketone in the reactions of substrates **2a**−**d**,**h**,**i**. With 1-*tert*-butylcyclopentanol (**2e**), 1-allylcyclopentanol (**2f**), and 1-benzylcyclopentanol (**2g**) formation of comparable amounts of the corresponding ring-opened iodoketones (7-iodo-2,2-dimethylheptan-3-one, 8-iodo-1-octen-4-one, and 6-iodo-1-phenylhexan-2-one, respectively), alkyl iodides (2-iodo-2-methylpropane, 3-iodopropene, and benzyl iodide, respectively), and cycloalkanones were instead observed.

In the 1-alkylcyclohexanol series (Table 3), exclusive formation of the corresponding ring-opened iodoketone was observed in the reactions of substrates **3a**,**b**,**h**,**i**. With 1-*tert*-butylcyclohexanol (**3e**) and 1-benzylcyclohexanol (**3g**), exclusive formation of the corresponding alkyl iodide (2-iodo-2-methylpropane and benzyl iodide, respectively) and cycloalkanone was instead observed. The reaction of 1-propylcyclohexanol (**3c**) led to the formation of 9-iodononan-4-one as major product accompanied by smaller amounts of 1-iodopropane and cyclohexanone. The reaction of 1-isopropylcyclohexanol (**3d**) led to the formation of 2-iodopropane and cyclohexanone as major products accompanied by a smaller amount of 8-iodo-2-methyloctan-3-one.

In the 1-alkylcycloheptanol series (Table 4), the reaction of 1-phenylcycloheptanol (**4h**) led to the exclusive formation of 7-iodo-1-phenylheptan-1-one. With 1-isopropylcycloheptanol (**4d**), 1-*tert*-butylcycloheptanol (**4e**), and 1-benzylcycloheptanol (**4g**), exclusive formation of the corresponding alkyl iodides (2-iodopropane, 2-iodo-2-methylpropane, and benzyl iodide, respectively) and cycloalkanones was instead observed. The reaction of 1-propylcycloheptanol (**4c**) led to the formation of comparable amounts of 10-iododecan-4-one, cycloheptanone, and 1-iodopropane as major products accompanied by smaller amounts of products (together accounting for ≈ 23% of the detected products) identified as 1-propyl-3-cyclohepten-1-ol, 1-propyl-4-cyclohepten-1-ol, and 4-iodo-1-propylcycloheptanol.

In the 1-alkylcyclooctanol series (Table 5), the reactions of 1-isopropylcyclooctanol (**5d**), 1-*tert*-butylcyclooctanol (**5e**), and 1-benzylcyclooctanol (**5g**) led to the exclusive formation of the corresponding alkyl iodides (2-iodopropane, 2-iodo-2-methylpropane, and benzyl iodide, respectively) and cycloalkanones. The reaction of 1-propylcyclooctanol (**5c**) led to the formation of 11-iodoundecan-4-one, cyclooctanone, and 1-iodopropane (together accounting only for ∼19% of the detected products), accompanied by greater amounts of products identified as 1-propyl-3-cycloocten-1-ol, 1-propyl-4-cycloocten-1-ol, and 4-iodo-1-propylcyclooctanol and by a smaller amount (∼2%) of a product which, on the basis of the GC−MS data, can be tentatively assigned to 6-iodo-1-propyl-4-cycloocten-1ol. With 1-phenylcyclooctanol (**5h**), formation of 8-iodo-1-phenyloctan-1-one as major product was observed, accompanied by comparable amounts of products identified as 1-phenyl-3-cycloocten-1-ol, 1-phenyl-4-cycloocten-1-ol, and 4-iodo-1-phenylcyclooctanol (together accounting for ∼43% of the detected products).

It is interesting to observe that the reactions of the 1-*tert*-butylcycloalkanols (**2e**−**5e**) led in all cases to significantly lower conversions than those observed in the reactions of the other substrates under the same experimental conditions. Conversion was found to increase by increasing irradiation time or, with **5e**, by increasing DIB and $I_2$ concentrations. Observations which suggest that in the presence of a bulky *tert*-butyl substituent formation of the intermediate hypoiodite by thermal reaction between DIB, $I_2$, and the alcohol is disfavored.

## Discussion

As mentioned above, ring-opening of cycloalkoxyl radicals to give $\omega$-formyl alkyl radicals is a reversible process

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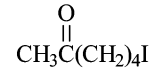
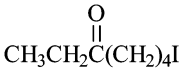
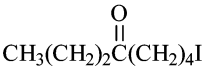
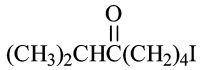
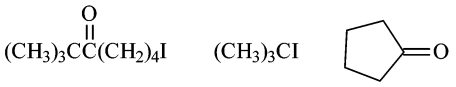
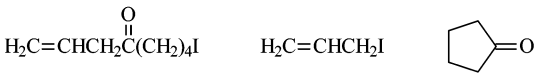
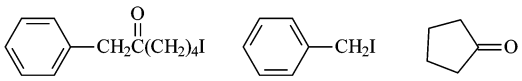
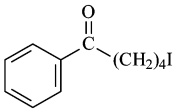
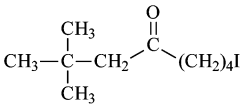
(22) Hook, S. C. W.; Saville, B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 589−593.
(23) The possibility that iodoalkane formation occurs through an iodine transfer step from the hypoiodite, precursor of the alkoxyl radical, should also be considered. We thank a reviewer for drawing our attention on this point.

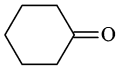
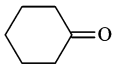
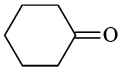
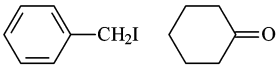
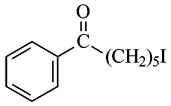
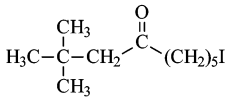
**TABLE 2. Product Distributions Observed after Irradiation of Ar-Saturated $CH_2Cl_2$ Solutions ($T$ = 20 °C) Containing 1-Alkylcyclopentanols (2a−i), DIB, and $I_2$[a]**

| Substrate | Products | Conversion (%) | Q[b] |
|---|---|---|---|
| **2a** (R = $CH_3$) |  | 56 | < 0.01[c] |
| **2b** (R = $CH_2CH_3$) |  | 45 | < 0.01[c] |
| **2c** (R = $CH_2CH_2CH_3$) |  | 55 | < 0.01[c] |
| **2d** (R = $CH(CH_3)_2$) |  | 73 | < 0.01[c] |
| **2e** (R = $C(CH_3)_3$) |  | 20<br>39[d] | 2.2 |
| **2f** (R = $CH_2CH{=}CH_2$) |  | 52 | 0.58 |
| **2g** (R = $CH_2C_6H_5$) |  | 49 | 1.03 |
| **2h** (R = $C_6H_5$) |  | 36 | < 0.01[c] |
| **2i** (R = $CH_2C(CH_3)_3$) |  | 44<br>83[e] | < 0.01[c] |

[a] [substrate] = 10 mM; [DIB] = 11 mM; [$I_2$] = 10 mM; $\lambda_{irr}$ = 480 nm; irradiation time = 5 min. [b] Ratio between C−R cleavage (cyclopentanone) and ring-opening products. [c] No C−R cleavage products detected. [d] Irradiation time = 15 min. [e] Irradiation time = 10 min.

(Scheme 2);[15] thus, for relative reactivity studies, conditions must be chosen in such a way that the follow-up reaction of the carbon-centered radical produced by ring opening is much faster than its cyclization. In the cyclobutoxyl and cyclopentoxyl radicals the equilibrium is strongly displaced to the fragmented carbon-centered radical (i.e., $K = k_o/k_c \gg 2000$ for the cyclopentoxyl radical) while a significantly smaller equilibrium constant ($K \gg 10$) has been measured for the cyclohexoxyl radical.[15a] No data are instead available for the cycloheptoxyl and cyclooctoxyl radicals for which, however, it should be taken into account that formation of seven- and eight-membered rings is usually disfavored as compared to five- and six-membered ones.[24] In this context, it is also important to point out that both the efficient trapping by iodine of the carbon-centered radical produced by ring opening (Scheme 4),[21,22] and the steric and electronic effects resulting from the presence of an alkyl

**TABLE 3. Product Distributions Observed after Irradiation of Ar-Saturated $CH_2Cl_2$ Solutions ($T$ = 20 °C) Containing 1-Alkylcyclohexanols (3a−e,g−i), DIB, and $I_2$[a]**

| Substrate | Products | Conversion (%) | Q[b] |
|---|---|---|---|
| **3a** ($R = CH_3$) | $CH_3C(=O)(CH_2)_5I$ | 47 | < 0.01[c] |
| **3b** ($R = CH_2CH_3$) | $CH_3CH_2C(=O)(CH_2)_5I$ | 61 | < 0.01[c] |
| **3c** ($R = CH_2CH_2CH_3$) | $CH_3(CH_2)_2C(=O)(CH_2)_5I$ $CH_3(CH_2)_2I$  | 63[e] | 0.06 |
| **3d** ($R = CH(CH_3)_2$) | $(CH_3)_2CHC(=O)(CH_2)_5I$ $(CH_3)_2CHI$  | 52 | 15.9 |
| **3e** ($R = C(CH_3)_3$) | $(CH_3)_3CI$  | 24<br>41[f] | > 200[d] |
| **3g** ($R = CH_2C_6H_5$) |  | 72 | > 200[d] |
| **3h** ($R = C_6H_5$) |  | 53 | < 0.01[c] |
| **3i** ($R = CH_2C(CH_3)_3$) |  | 46[g]<br>80 | < 0.01[c] |

[a] [substrate] = 10 mM; [DIB] = 11 mM; [$I_2$] = 10 mM; $\lambda_{irr}$ = 480 nm; irradiation time = 10 min. [b] Ratio between C−R cleavage (cyclohexanone) and ring-opening products. [c] No C−R cleavage products detected. [d] No ring-opening products detected. [e] Traces (<1%) of a product assigned by GC−MS analysis to 1-propyl-3-cyclohexenol were also detected. [f] Irradiation time = 30 min. [g] Irradiation time = 5 min.

substituent bound to the carbonyl group,[25,26] should strongly depress the relative importance of the cyclization reaction. Accordingly, in the reactions of substrates **3d** and **4c**, no increase in the relative amount of ring-opening products was observed when the concentration of iodine was increased by a factor 5. Results which confirm that, under the experimental conditions employed, cyclization of the carbon-centered radical produced by ring opening does not compete with its reaction with iodine. On the basis of these considerations, it is reasonable to conclude that reversibility should not influence to any significant extent the intramolecular selectivity (competition between ring opening and C−R cleavage) in the C−C $\beta$-scission reactions of the 1-alkylcycloalkoxyl radicals reported above.

Starting from the 1-alkylcyclobutanols, the results of Table 1 show that the exclusive fragmentation pathway of the 1-allylcyclobutoxyl and 1-benzylcyclobutoxyl radicals, generated, respectively, from substrates **1f** and **1g**, is cyclobutane ring opening (Scheme 5), and even though C−R cleavage would lead to relatively stable radicals ($CH_2$=$CHCH_2^\bullet$ from **1f** and $PhCH_2^\bullet$ from **1g**),[27] no evidence for the formation of products deriving from this pathway was obtained, a behavior which suggests that with 1-alkylcyclobutoxyl radicals the fragmentation regioselectivity is governed by the very high ring strain associated with a four-membered ring.[16]

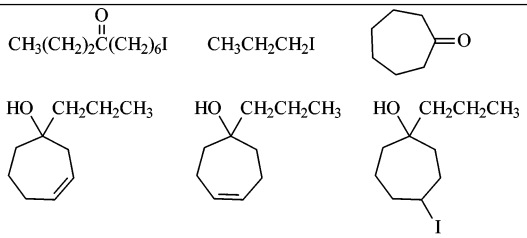
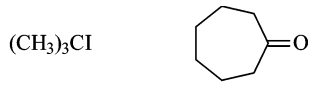
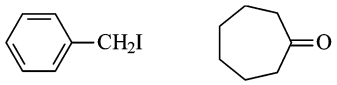
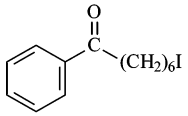
(24) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1−111. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

(25) Henry, D. J.; Coote, M. L.; Gómez-Balderas, R.; Radom, L. *J. Am. Chem. Soc.* **2004**, *126*, 1732−1740.

(26) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−974.

(27) Wayner, D. D. M.; Griller, D. In *Advances in Free Radical Chemistry;* Tanner, D. D., Ed.; JAI Press: Greenwich, 1990; Vol. 1, p 159.

**TABLE 4. Product Distributions Observed after Irradiation of Ar-Saturated $CH_2Cl_2$ Solutions ($T$ = 20 °C) Containing 1-Alkylcycloheptanols (4c−e,g,h), DIB, and $I_2$[a]**

| Substrate | Products | Conversion (%) | Q[b] |
|---|---|---|---|
| **4c** (R= $CH_2CH_2CH_3$) |  | 64 | 0.75[c] |
| **4d** (R = $CH(CH_3)_2$) |  | 49[d] | > 200[e] |
| **4e** (R = $C(CH_3)_3$) |  | 27<br>33[d] | > 200[e] |
| **4g** (R = $CH_2C_6H_5$) |  | 61[f] | > 200[e] |
| **4h** (R = $C_6H_5$) |  | 49 | < 0.01[g] |

[a] [substrate] = 10 mM; [DIB] = 11 mM; [$I_2$] = 10 mM; $\lambda_{irr}$ = 480 nm; irradiation time = 5 min. [b] Ratio between C−R cleavage (cycloheptanone) and ring-opening products. [c] Ratio between cycloheptanone and 10-iododecan-4-one. [d] Irradiation time = 10 min. [e] No ring-opening products detected. [f] Irradiation time = 8 min. [g] No C−R cleavage products detected.

The situation changes as we move to the 1-alkylcyclopentanols. The results of Table 2 show that while the exclusive fragmentation pathway of the alkoxyl radicals generated from substrates **2a**−**d**,**h**,**i** is cyclopentane ring opening, competition between ring opening and C−R cleavage is instead observed for the alkoxyl radicals generated from substrates **2e**−**g**. This result indicates that the importance of the C−R cleavage pathway increases with the stability of the alkyl radical R•. However, since it is well-known that both the allyl and benzyl radicals are significantly more stable than the *tert*-butyl radical,[28] the observation that the importance of the C−R cleavage pathway decreases on going from the 1-*tert*-butylcyclopentoxyl radical (for which **Q** = 2.2) to the 1-benzylcyclopentoxyl and 1-allylcyclopentoxyl ones (for which **Q** = 1.03 and 0.58, respectively) indicates that release of ring strain and alkyl radical stability are not the only factors which govern the fragmentation regioselectivity, but also steric effects are likely to play a significant role.

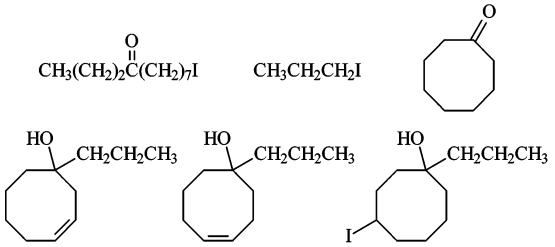
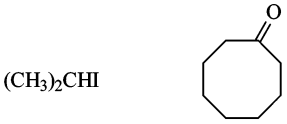
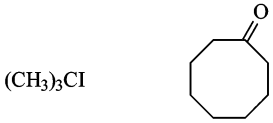
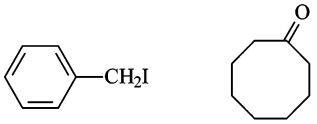
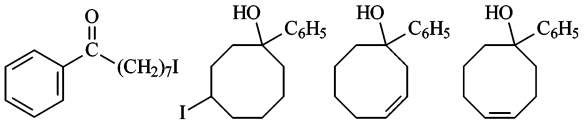
As we move to the 1-alkylcyclohexanol series, the results of Table 3 show that now exclusive or predominant ring opening is observed for the alkoxyl radicals generated from substrates **3a**−**c**,**h**,**i** (for which R = $CH_3$, $CH_3CH_2$, $CH_3CH_2CH_2$, Ph and $(CH_3)_3CCH_2$, respectively). With alkoxyl radicals derived from substrates **3d**, **3e**, and **3g** (R = $(CH_3)_2CH$, $(CH_3)_3C$ and $PhCH_2$, respectively), predominant or exclusive C−R cleavage is instead observed. Clearly, in a strain-free system the fragmentation regioselectivity is essentially governed by the stability of the radical formed. Unfortunately, the results obtained for the 1-alkylcyclohexoxyl radicals do not provide information on the role of steric effects because no evidence for the formation of ring opening products was obtained in the reactions of the 1-*tert*-butylcyclohexoxyl and 1-benzylcyclohexoxyl radicals.

Interestingly, comparison between the results obtained for the 1-benzylcyclobutoxyl, 1-benzylcyclopentoxyl and 1-benzylcyclohexoxyl radicals (for which **Q** < 0.01, **Q** = 1.03, and **Q** > 200, respectively) indicates that the ring opening reaction of cycloalkoxyl radicals follows the order: cyclobutoxyl > cyclopentoxyl > cyclohexoxyl, in line with the ring strain associated with four-, five-, and six-membered rings[16] and with the computed activation energies for the ring opening reactions of cycloalkoxyl radicals (7.7, 15.4, and 20.7 kcal/mol, for the cyclobutoxyl, cyclopentoxyl, and cyclohexoxyl radical, respectively).[8]

In the 1-alkylcycloheptanol series, the results of Table 4 show that exclusive ring opening is observed only for the 1-phenylcycloheptoxyl radical in line with the relatively low stability of the phenyl radical which disfavors

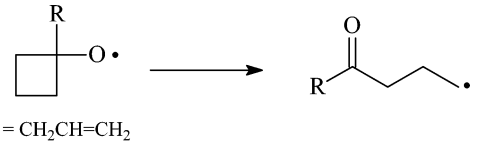
(28) The following homolytic bond dissociation energies have been determined for $(CH_3)_3C-H$, $PhCH_2-H$ and $CH_2=CHCH_2-H$: 93.6, 87.9, and 86.8 kcal mol$^{-1}$, respectively (see ref 27).

**TABLE 5. Product Distributions Observed after Irradiation of Ar-Saturated $CH_2Cl_2$ Solutions ($T$ = 20 °C) Containing 1-Alkylcyclooctanols (5c−e,g,h), DIB, and $I_2$[a]**

| Substrate | Products | Conversion (%) | Q[b] |
|---|---|---|---|
| **5c** (R= $CH_2CH_2CH_3$) |  | 58[c] | 0.44[d] |
| **5d** (R = $CH(CH_3)_2$) |  | 54[e] | > 200[f] |
| **5e** (R = $C(CH_3)_3$) |  | 22<br>23[e]<br>37[e,g] | > 200[f] |
| **5g** (R = $CH_2C_6H_5$) |  | 79[h] | > 200[f] |
| **5h** (R = $C_6H_5$) |  | 22 | < 0.01[i] |

[a] [substrate] = 10 mM; [DIB] = 11 mM; [$I_2$] = 10 mM; $\lambda_{irr}$ = 480 nm; irradiation time = 5 min. [b] Ratio between C−R cleavage (cyclooctanone) and ring-opening products. [c] A small amount (~2%) of a product assigned by GC−MS analysis to 6-iodo-1-propyl-4-cyclooctenol was also detected. [d] Ratio between cyclooctanone and 11-iodoundecan-4-one. [e] Irradiation time = 10 min. [f] No ring-opening products detected. [g] [substrate] = 10 mM; [DIB] = 40 mM; [$I_2$] = 20 mM. [h] Irradiation time = 8 min. [i] No C−R cleavage products detected.

**SCHEME 5**



R = $CH_2CH{=}CH_2$
R = $CH_2C_6H_5$

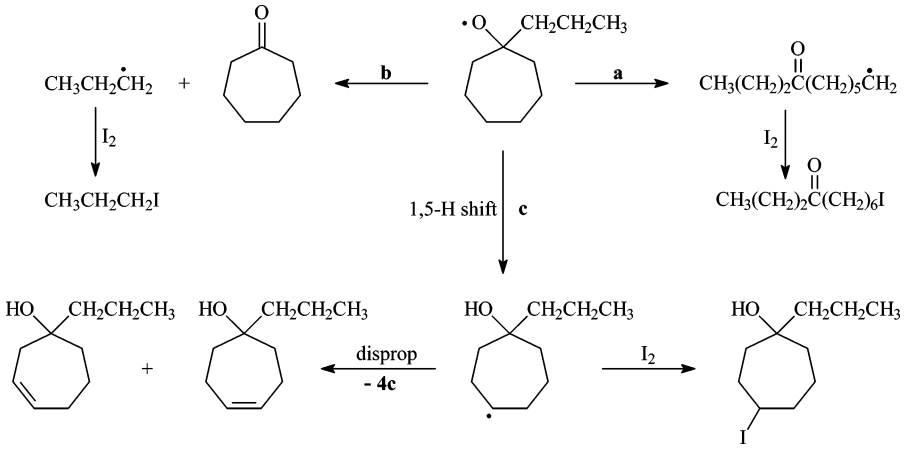
the C−Ph bond cleavage pathway.[27] With alkoxyl radicals derived from substrates **4d**,**e**,**g** (R = $(CH_3)_2CH$, $(CH_3)_3C$, and $PhCH_2$, respectively) exclusive C−R cleavage is observed. Competition between ring opening and C−R cleavage is instead observed for the 1-propylcycloheptoxyl radical as shown by the formation of comparable amounts of 10-iododecan-4-one (Scheme 6, path a), cycloheptanone and 1-iodopropane (path b). In this reaction, formation of smaller amounts of products identified as 1-propyl-3-cyclohepten-1-ol, 1-propyl-4-cyclohepten-1-ol, and 4-iodo-1-propylcycloheptanol was also observed.

Formation of the latter products can be rationalized in terms of an intramolecular 1,5-hydrogen atom transfer (1,5-HAT) from the cycloheptane ring in the intermediate alkoxyl radical to give a carbon centered radical (path c). This radical can be trapped by iodine forming 4-iodo-1-propylcycloheptanol or disproportionate to give the two isomeric 1-propylcycloheptenols.

The observation that in the 1-propylcycloheptoxyl radical 1,5-HAT competes with C−C $\beta$-scission whereas with the corresponding cyclohexoxyl radical (derived from **3c**) exclusive $\beta$-scission is observed can be explained in terms of the greater flexibility of the former radical[16,30] which allows the achievement of the quasilinear arrangement between the oxygen, the migrating hydrogen, and the carbon center, proposed for the transition state for 1,5-HAT.[29,31] The cyclohexoxyl radical would have instead to achieve an unfavorable boat conformation in order to undergo 1,5-HAT.[29] Another factor in this respect may be represented by differences in the rate of ring-opening of the 1-propylcyclohexoxyl and 1-propylcycloheptoxyl radicals, but unfortunately the experimental data do not

(29) Dorigo, A. E.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 1650−1664.
(30) Wiberg, K. B. *J. Org. Chem.* **2003**, *68*, 9322−9329.
(31) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 2195−2197.

**SCHEME 6**




allow a direct comparison between the reactivities of the two radicals.[32]

The observation that with the 1-propylcycloheptoxyl radical no products deriving from a 1,5-HAT reaction from the propyl group are formed indicates that intramolecular HAT occurs significantly faster from the cycloheptane ring than from the propyl side chain, in line with the well-known preference for abstraction at more highly substituted carbon atoms.[18,33,34]

Finally, the observation that no products deriving from a 1,5-HAT reaction are formed with the 1-phenylcycloheptoxyl radical can be explained in terms of an increase in the rate of ring opening determined by the presence of a phenyl substituent,[35] which accordingly decreases the relative importance of the 1,5-HAT pathway.

In the 1-alkylcyclooctanol series, the results of Table 5 show that with the alkoxyl radicals derived from substrates **5d**, **5e**, and **5g** (R = $(CH_3)_2CH$, $(CH_3)_3C$ and $PhCH_2$, respectively) exclusive C−R cleavage is observed. Competition between ring opening and C−R cleavage is instead observed for the 1-propylcyclooctoxyl radical as shown by the formation of comparable amounts of 11-iodoundecan-4-one, cyclooctanone and 1-iodopropane. With this radical however, $\beta$-scission reactions appear to be minor pathways as clearly shown by the formation of significant amounts of products identified as 1-propyl-3-cycloocten-1-ol, 1-propyl-4-cycloocten-1-ol, and 4-iodo-1-propylcyclooctanol. In analogy, with the results discussed above for the 1-propylcycloheptoxyl radical (Scheme 6), formation of these products can be again rationalized in terms of an intramolecular 1,5-HAT from the cyclooctane ring in the intermediate alkoxyl radical. Competition between ring opening and 1,5-HAT is observed also with the 1-phenylcyclooctoxyl radical, as shown by the formation of 8-iodo-1-phenyloctan-1-one as major product accompanied by comparable amounts of products identified as 1-phenyl-3-cycloocten-1-ol, 1-phenyl-4-cycloocten-1-ol, and 4-iodo-1-phenylcyclooctanol. Again, as discussed above for the cycloheptoxyl radicals, the presence of a phenyl group should determine an increase in the relative importance of the ring opening pathway as compared to the intramolecular hydrogen atom transfer one.[35] The observation that in both the 1-propylcyclooctoxyl and 1-phenylcyclooctoxyl radicals the relative importance of the 1,5-HAT pathway is significantly higher than in the corresponding cycloheptoxyl radicals points toward a more favorable geometry for the intramolecular 1,5-HAT reaction in the former radicals.[16,30,38]

On the basis of the comparable strain energies associated with seven- and eight-membered rings,[16] and of the similar values of the **Q** ratio measured for the fragmentation reactions of the 1-propylcycloheptoxyl and 1-propylcyclooctoxyl radicals (0.75 and 0.44, respectively), it seems reasonable to suggest that the two radicals undergo ring-opening with similar rates.

Finally, in full agreement with the results presented above are also the results obtained previously in the photolysis of a series of 1-vinylcycloalkanols in the presence of DIB and $I_2$.[39] The product distributions shown in Scheme 7 indicate that the intermediate alkoxyl radicals undergo competition between ring opening and intramolecular addition to the double bond depending on ring size, while products deriving from C−R bond cleavage are not observed, as expected on the basis of the relatively low stability of the vinyl radical.[27]

Thus, ring-opening is observed only for the 1-vinylcyclopentoxyl radical, while for the other radicals the rate of intramolecular addition is significantly faster than that

(32) In a first approximation, by assuming similar rate constants for C−R bond cleavage in the 1-propylcyclohexoxyl and 1-propylcycloheptoxyl radicals, comparison between the **Q** ratios obtained from the reactions of the two radicals (**Q** = 0.06 for the 1-propylcyclohexoxyl radical and **Q** = 0.75 for the 1-propylcycloheptoxyl one) suggests that ring-opening of the former radical is faster than that of the latter one, a finding which, however, is in contrast with the significantly greater ring strain associated to a seven-membered ring as compared to a six-membered one. Moreover, such an assumption does not take into account that the differences in strain between the radical and the product cycloalkanone should be significantly different in the two systems (see ref 16), and accordingly different rates of C−R cleavage can be reasonably expected for the two radicals.

(33) Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525−538.

(34) Weavers, R. T. *J. Org. Chem.* **2001**, *66*, 6453−6461.

(35) For example an increase between 10 and 20 times (depending on solvent) in the rate constant for C-Me $\beta$-scission is observed on going from the *tert*-butoxyl radical (see ref 36) to the cumyloxyl one (see refs 19 and 37).

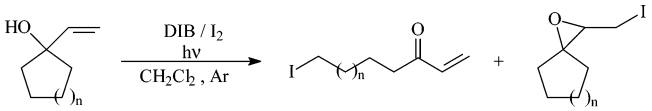
(36) (a) Tsentalovich, Y. P.; Kulik, L. V.; Gritsan, N. P.; Yurkovskaya, A. V. *J. Phys. Chem. A* **1998**, *102*, 7975−7980. (b) Weber, M.; Fischer, H. *J. Am. Chem. Soc.* **1999**, *121*, 7381−7388.

(37) Baciocchi, E.; Bietti, M.; Salamone, M.; Steenken, S. *J. Org. Chem.* **2002**, *67*, 2266−2270.

(38) Petrović, G.; Čeković, Z. *Tetrahedron* **1999**, *55*, 1377−1390.

(39) (a) Galatsis, P.; Millan, S. D. *Tetrahedron Lett.* **1991**, *32*, 7493−7496. (b) Galatsis, P.; Millan, S. D.; Faber, T. *J. Org. Chem.* **1993**, *58*, 1215−1220.

**SCHEME 7**




for ring opening. As a matter of comparison, an analogous trend has been observed with the alkoxyl radicals formed from the 1-benzylcycloalkanols (substrates **2g**−**5g**), where competition between ring-opening and C−R cleavage is observed only for the 1-benzylcyclopentoxyl radical, whereas with the other 1-benzylcycloalkoxyl radicals exclusive C−R cleavage occurs. Interestingly, comparison of the results obtained for the 1-vinylcyclopentoxyl radical[39a] with those obtained for the 1-allylcyclopentoxyl and 1-benzylcyclopentoxyl ones suggests that the rate of intramolecular addition to the double bond in the former radical is comparable with those for C−R cleavage in the latter ones.

In conclusion, the results presented above clearly show that in the fragmentation reactions of 1-alkylcycloalkoxyl radicals the regioselectivity is governed by the interplay between release of ring strain associated to ring opening and stability of the alkyl radical formed by C−R cleavage, even though in the presence of bulky substituents such as a *tert*-butyl group steric effects appear to play a role. The importance of the ring-opening pathway decreases by increasing ring size, and, with the exclusion of the cyclobutoxyl radicals, by increasing the stability of R•. Accordingly, the rates of ring-opening follow the order cyclobutoxyl > cyclopentoxyl > cyclohexoxyl, in line with the ring strain associated with four-, five-, and six-membered rings. Unfortunately, the results obtained do not allow a direct comparison between the rates of ring-opening of the cyclohexoxyl, cycloheptoxyl, and cyclooctoxyl radicals, pointing however toward similar rates of ring-opening for the latter radicals (cycloheptoxyl ≈ cyclooctoxyl).

With the 1-propylcycloheptoxyl, 1-propylcyclooctoxyl, and 1-phenylcyclooctoxyl radicals $\beta$-scission competes with an intramolecular 1,5-HAT reaction, a behavior that has been interpreted in terms of the possibility of achieving a more favorable geometry in the transition state for intramolecular 1,5-HAT in cycloheptoxyl and cyclooctoxyl radicals as compared to cyclohexoxyl ones.

## Experimental Section

**Materials.** (Diacetoxy)iodobenzene (DIB) and iodine were of the highest commercial quality available. Commercial samples of 1-methylcyclopentanol and 1-methylcyclohexanol were used without further purification. Details of the synthesis of the other 1-alkylcycloalkanols are given in the Supporting Information. The purity of the 1-alkylcycloalkanols employed in the product studies was always ≥99%.

**Product Analyses.** All the reactions were carried out under an argon atmosphere. Dichloromethane was purified prior to use by column chromatography over basic alumina. Irradiations were performed with visible light (10 × 15 W lamps with emission between 400 and 550 nm, $\lambda_{max} \approx 480$ nm). The reactor was a cylindrical flask equipped with a water-cooling jacket thermostated at 20 °C. Irradiation times were chosen in such a way as to avoid complete substrate consumption. In a typical experiment, a solution of the alcohol (10 mM) in $CH_2Cl_2$ (5 mL) containing (diacetoxy)iodobenzene (11 mM) and iodine (10 mM) was irradiated for times ranging between 1 and 30 min under Ar bubbling. The reaction mixture was then poured into water and extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were washed with a 10% aqueous thiosulfate solution (2 × 30 mL) and water (2 × 30 mL) and dried over anhydrous sodium sulfate. Reaction products were generally identified by GC−MS and $^1$H NMR (for details see the Supporting Information) and quantitatively determined by GC and $^1$H NMR (comparison with authentic samples for the cycloalkanones and alkyl iodides). In the reactions of substrates **4c**, **5c**, and **5h**, the reaction products were not isolated and their structures were assigned on the basis of the GC−MS and, when possible, $^1$H NMR data. The quantitative analysis of the reaction mixture was performed by GC and by $^1$H NMR after removal of the solvent at atmospheric pressure. In both cases, bibenzyl was used as internal standard. In the latter method, the product $RC(O)(CH_2)_nCH_2I$ (where $n = 2-6$, and R = Me, Et, Pr, *i*-Pr, *t*-Bu, benzyl, allyl, Ph, and neopentyl) was quantitatively determined through the characteristic $CH_2I$ signal at 3.17 ppm. Good to excellent mass balances (≥ 85%) were obtained in all experiments. With the exception of the 1-benzylcycloalkanols for which both benzyl iodide and cycloalkanone were quantitatively determined, no quantitative determination of the alkyl iodide was carried out for the reactions of the other substrates. Thus, the ratio **Q** between R cleavage and ring-opening products was generally determined from the amounts of cycloalkanone and ring-opened iodinated ketone formed. Two to four experiments were carried out for each substrate showing excellent reproducibility.

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**Supporting Information Available:** Details on the synthesis and characterization of the 1-alkylcycloalkanols and of their reaction products (GC−MS and $^1$H NMR data). This material is available free of charge via the Internet at http://pubs.acs.org.

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