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Radical oxygenations with inorganic radicals: can hydroxyl radicals ($HO^\bullet$) act as donors of oxygen atoms?

Uta Wille*

Institut für Organische Chemie der Christian-Albrechts-Universität zu Kiel, Olshausenstraße 40, 24098 Kiel, Germany

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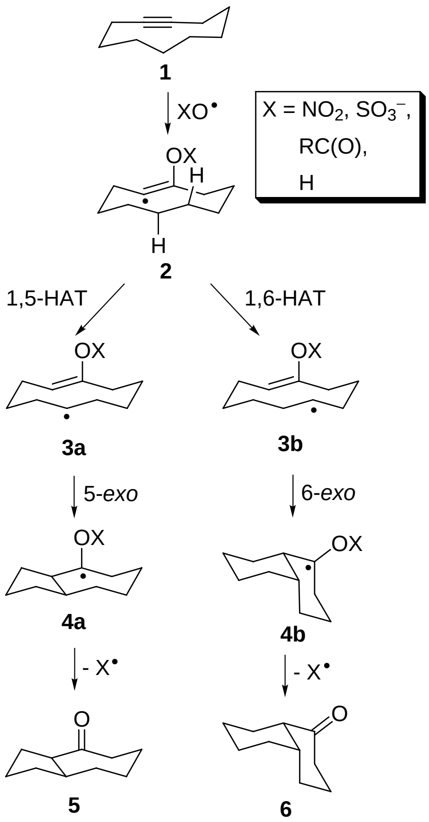
Abstract—Hydroxyl radicals ($HO^\bullet$) were shown to act, upon addition to the C–C triple bond in cyclic and open-chain alkynes, as oxygen atom donors in an oxidative radical cyclization sequence. © 2002 Elsevier Science Ltd. All rights reserved.

The highly reactive hydroxyl radical ($HO^\bullet$), which could also naturally occur in the troposphere[1] or in cells,[2] is probably one of the most extensively studied radical species. Since it can react with organic substrates either by hydrogen atom abstraction or by addition to aromatic and aliphatic π-systems, $HO^\bullet$ has been frequently applied to organic synthesis.[3] The addition reactions of this electrophilic radical to C–C double bonds are generally extremely fast and proceed with rates near the diffusion limit.[4] In this paper it is shown that $HO^\bullet$ possesses a so far unknown, mechanistically interesting feature, as it could also act as a donor of oxygen atoms in its reactions with alkynes.

In previous publications, we reported on a novel radical oxygenation, which was initiated by addition of an inorganic[5] or organic oxygen-centered radical $X–O^\bullet$ (with $X = NO_2$,[6a–d] SO_3^-,[6e] RC(O)[6f]) to C–C triple bonds in cyclic and open-chain alkynes and alkynones. The mechanism of the cyclization sequence is shown in Scheme 1 for the exemplary reaction with cyclodecyne **1**. After the initial radical addition two subsequent transannular steps occur: (i) a 1,5- or 1,6-hydrogen atom abstraction (HAT), **2**→**3a**,**b**;[7] and (ii) a 5-*exo* or 6-*exo* radical cyclization, **3a**,**b**→**4a**,**b**. The reaction cascade is terminated by release of a radical $X^\bullet$ under formation of the carbonyl group in the *cis*-fused bicyclic ketones **5** and **6**. Thus, in this sequence the radical $X–O^\bullet$ formally acts as a donor of oxygen atoms. Since the $X^\bullet$ released is relatively unreactive compared with $X–O^\bullet$ in all cases studied by us so far, and an initiation of a further radical reaction by $X^\bullet$ was never observed, this radical cyclization is of non-chain type. The success of this radical oxygenation, which proceeded with good to excellent yields in the case of the reaction of **1** with $NO_3^\bullet$, $SO_4^{\bullet -}$ or acyloxyl radicals $RC(O)O^\bullet$, respectively,[6] was expected to be dependent



Scheme 1. Proposed mechanism for the reaction of cyclodecyne **1** with oxygen-centered radicals $XO^\bullet$.

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* Tel.: +49-431-8801179; fax: +49-431-8801558; e-mail: uwille@oc.uni-kiel.de

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on the ease of the homolytic cleavage of the X–O bond in the final step and thus on the ability of the radical $X^\bullet$ to act as a leaving group.[8]

In order to obtain additional mechanistic insights into this radical oxygenation and, possibly, to enlarge the pool of radicals with similar properties as oxygen atom donors, it was decided to study the scope of $HO^\bullet$ in this radical cyclization. From the mechanistic point of view, this investigation seemed to be an exceptional challenge because: (i) hydrogen atom abstraction from the activated allylic position in **1** by $HO^\bullet$ might compete seriously or even dominate over $HO^\bullet$ addition to the C–C triple bond; and (ii) the termination step might be disfavored, because an O–H bond is relatively stable, and $H^\bullet$ is only a poor leaving group.[8]

Using the reaction with cyclodecyne **1** as a model system,[9] different methods for $HO^\bullet$ generation were employed. However, GC analysis revealed that the reaction of **1** in the presence of either the Fenton redox couple Fe^{2+}/H_2O_2[3b] or Barton's Gif oxygenation system $CoAgg^{II}$ or $CoAgg^{III}$, respectively,[10] gave only poor yields of **5** and **6** (data not shown), although they are both known to be versatile sources for $HO^\bullet$.[11,12] In contrast, when $HO^\bullet$ was generated in a homogeneous system by photolysing *N*-hydroxy-2-thiopyridone **7** in acetonitrile (Scheme 2), the ketones **5** and **6** could be obtained with a 1.2:1 ratio in acceptable combined yield, which depended strongly on the reaction conditions (Table 1).[13,14] The comparatively low yields of the ketones obtained in the reaction with equimolar or excess radical precursor **7** (entries 1–3) led to the suggestion that a fast trapping of the highly reactive $HO^\bullet$ by excess **1** could lead to a significant improvement. With a ratio of [**7**]/[**1**] in the range 0.3–0.1, a satisfactory combined yield of around 60% of **5** and **6** could be obtained (entries 4, 5, and 7). No significant formation of byproducts was observed under these conditions in the GC. The generation of $HO^\bullet$ through an alternative pathway by photolyzing the thiazolethione **9**[15] (Scheme 2) did not lead to a further improvement of the product yield under comparable reaction conditions (entry 8).

Possible interfering radical–radical or hydrogen abstraction reactions by $HO^\bullet$ could be the reason for the lower yields of **5** and **6** in the case of excess or equimolar amounts of radical precursor **7** and thus of $HO^\bullet$, especially if the total concentration of reactants was high (entry 1).[16] To explore whether a major part of $HO^\bullet$ might get lost through a reaction with the solvent acetonitrile, e.g. by hydrogen abstraction, an experiment was performed in tetrachloromethane (entry 6). However, the even lower combined yield of **5** and **6** achieved under these conditions indicated that such a reaction pathway could be excluded. On the contrary, the higher yields obtained in acetonitrile may suggest a slight stabilization of $HO^\bullet$ by polar effects.

Even though the yield of the ketones **5** and **6** in the $HO^\bullet$-induced oxidative cyclization of **1** is possibly not high enough for a general preparative application (in contrast to the respective reactions of $NO_3^\bullet$, $SO_4^{\bullet-}$ and $RC(O)O^\bullet$), this reaction is mechanistically very interesting. Regardless of the strength of a O–H bond and the low ability of $H^\bullet$ to act as a leaving group, more than 50% of the hydroxyl radicals generated by photolysis of **7**, initiated and underwent the cyclization cascade according to the mechanism depicted in Scheme 1.

Anyway, the possibility of an alternative reaction pathway needs to be considered. Since $HO^\bullet$ is a strong

Table 1. Experimental data and results of the reaction of $HO^\bullet$ with cyclodecyne **1**[a]

Entry	$HO^\bullet$ source (mM)	**1** (mM)	$[HO^\bullet]^b/[\mathbf{1}]$	Yield **5**+**6**[c,d]
1	200.0 (**7**)	108.0	1.85	14% (15%)
2	28.9 (**7**)	14.0	2.06	21% (35%)[e]
3	10.1 (**7**)	10.4	0.97	21% [21%]
4	4.1 (**7**)	13.1	0.31	17% [53%]
5	3.4 (**7**)	20.5	0.17	9% [63%]
6	2.5 (**7**)	15.6	0.16	8% [47%][f]
7	1.3 (**7**)	12.8	0.10	6% [56%]
8	1.6 (**9**)	15.8	0.10	4% [35%]

[a] The experiments were performed in 10 mL of acetonitrile unless otherwise stated. Irradiation time: 60–90 min.

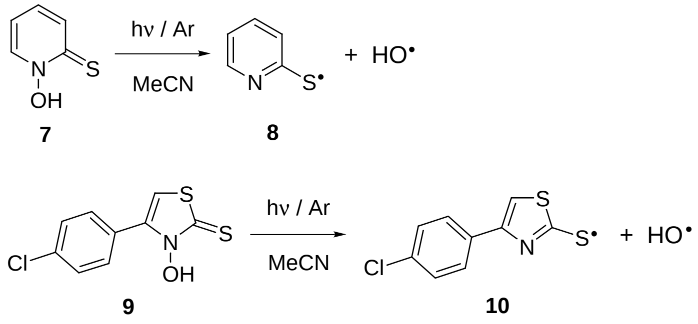
[b] A 100% conversion of **7** or **9**, respectively, to $HO^\bullet$ is assumed.

[c] Combined yield determined by GC using *n*-hexadecane as internal standard.

[d] Yield with respect to the starting concentration of **1** or to consumed **1** (in parentheses). Data in brackets: yield with respect to the concentration of the radical precursor **7** or **9**.

[e] In 80 mL of acetonitrile; 4 h irradiation time.

[f] In 10 mL of tetrachloromethane.



Scheme 2. Photochemical generation of $HO^\bullet$.

hydrogen abstracting agent, the reaction sequence might also be initiated by abstraction of an activated allylic hydrogen atom (Scheme 3). A 1,5-HAT in **11** leads to the radical **12** with the unpaired electron located opposite to the C–C triple bond. A subsequent 5-*exo* or 6-*exo* radical cyclization could give the vinyl radicals **13a**,**b**, which might be trapped by recombination with $HO^\bullet$ to yield the enols **14a**,**b**. The latter may finally tautomerize into the ketones **5** and **6**. Although this proposed alternative mechanism appears to be plausible, there are several arguments against its occurrence in this reaction. According to Scheme 3 formation of the ketones **5** and **6** would require 2 equiv. of $HO^\bullet$ per molecule **1**. Despite the assumption that the radical recombination of **13** with $HO^\bullet$ should proceed without a significant activation barrier, this step is a kinetically disfavored second-order process, which cannot compete with the reaction of $HO^\bullet$ with the excess component **1**. On the contrary, the yields of **5** and **6** should be expected to be significantly higher, if $HO^\bullet$ would be used in equimolar or excess amounts. The data in Table 1 clearly demonstrate that this was not the case. In addition, the tautomerism **14**→**5**,**6** is a thermodynamic process, which should lead to formation of at least a mixture of *cis* and *trans* isomers of the products, supposedly with a preferred formation of the thermodynamically more stable *trans* compounds. The observed exclusive formation of the bicyclic ketones **5** and **6** with a thermodynamically less stable *cis* fusion is in accordance with the kinetically controlled radical cyclization shown in Scheme 1.[17]

The $HO^\bullet$-induced radical oxygenation was also applied to the cyclization of an open-chain alkyne (Scheme 4). The tetrahydrofuran **16** was diastereoselectively formed through a cyclization cascade after initial addition of $HO^\bullet$ at the sterically less hindered site of the C–C triple bond in the alkynyl ether **15**, in analogy to the mechanism in Scheme 1.[18] However, the low yield of **16** indicates the occurrence of competing processes, possibly hydrogen abstractions by $HO^\bullet$ from the activated positions α to the ether oxygen.[16]

To conclude, it is demonstrated for the first time that $HO^\bullet$ possesses an additional interesting feature, as it can also act as a donor of oxygen atoms in the addition reaction with alkynes bearing no activated hydrogen atoms. The fate of the $H^\bullet$ released was not examined, but it may be assumed that, besides hydrogen abstraction from the solvent or from **1**, $H^\bullet$ could initiate formation of further $HO^\bullet$ through addition at the thione moiety in **7** and **9**, respectively, thus starting a radical-chain process (not shown).

Acknowledgements

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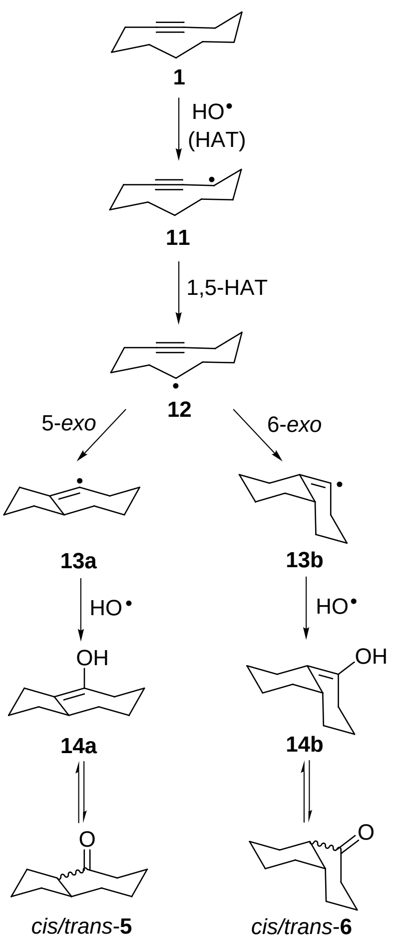
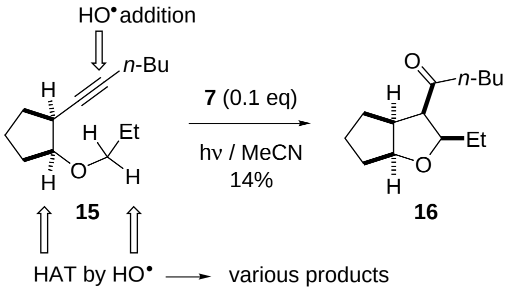


Scheme 3. Alternative reaction mechanism.



Scheme 4. Reaction of $HO^\bullet$ with the open-chain alkyne **15** (yield with respect to **7**).

References

1. $HO^\bullet$ is formed in the troposphere by the reaction: $O^*(^1D)+H_2O \rightarrow 2\ HO^\bullet$. For a general overview see: Wayne, R. P. *Chemistry of Atmospheres*, 2nd ed.; Clarendon Press: Oxford, 1991; pp. 214–275.
2. Absorption of UV radiation by the water could lead to formation of $HO^\bullet$ in cells, where it can produce non-specific strand cleavage. For a recent review see: Pogozelski, W. K.; Tullius, T. D. *Chem. Rev.* **1998**, *98*, 1089–1107.
3. For examples of the synthetic application of $HO^\bullet$, see: (a) Kyriacou, D. *Modern Electroorganic Chemistry*; Springer:

Berlin, 1994; pp. 172–174; (b) *Gmelin Handbuch der Anorganischen Chemie: Sauerstoff, Lieferung 8*, 8th ed.; Gmelin Institut für Anorganische Chemie der Max-Planck-Gesellschaft zur Förderung der Wissenschaften, Ed.; Verlag Chemie GmbH: Weinheim, 1968; pp. 2527–2600.

4. Leffler, J. E. *An Introduction to Free Radicals*; John Wiley and Sons: New York, 1993; pp. 116–121. The rate constants for addition or hydrogen atom abstraction reactions of activated hydrogens by $HO^{\bullet}$ are in the range 10^{9}–10^{10} M^{-1} s^{-1} (in aqueous solution). From the data given in Ref. 3b, it appears that addition of $HO^{\bullet}$ to π-systems is slightly faster than abstraction.
5. Although there is some controversy about the definition of inorganic for a chemical species, which contains no carbon atoms, this term shall be used here for the sake of clarity.
6. (a) Wille, U.; Plath, C. *Liebigs Ann./Recueil* **1997**, 111–119; (b) Wille, U.; Lietzau, L. *Tetrahedron* **1999**, *55*, 10119–10134; (c) Lietzau, L.; Wille, U. *Heterocycles* **2001**, *55*, 377–380; (d) Wille, U.; Lietzau, L. *Tetrahedron* **1999**, *55*, 11465–11474; (e) Wille, U. *Org. Lett.* **2000**, *2*, 3485–3488; (f) Wille, U. *J. Am. Chem. Soc.* **2002**, *124*, 14–15.
7. Correctly, by taking both possible directions of enumeration in the carbocyclic ring into account, the transannular 1,5-HAT of **2** to **3a** should be considered as a 1,5/1,7-HAT. For the sake of clarity, the nomenclature of these transannular radical reactions is based on the most probable process, e.g. 1,5- or 1,6-HAT, respectively. See: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley-Masson: Chichester, 1995; p. 52.
8. Related bond dissociation energies in kJ mol^{-1}: O–H (in primary alcohols): ca. 440; $O–NO_2$: 204; $O–SO_2$: 403; *CRC Handbook of Chemistry and Physics*, 63rd ed.; Weast, R. C.; Astle, M. J., Eds.; CRC Press: Boca Raton, 1982; pp. F196–200. Semiempirical calculations revealed an activation barrier of 5.5 kJ mol^{-1} for the homolytic cleavage of the $R_2C^{\bullet}O–NO_2$ bond in the final fragmentation step in Scheme 1.[6a]
9. Because of their strong transannular interactions, medium-sized cycloalkynes are appropriate model substrates to study the scope of this novel type of radical cyclizations, since the subsequent reaction steps are preferred to proceed intramolecularly.[6a,e,f]
10. $CoAgg^{II}$: Fe^{3+}/H_2O_2, pyridine/AcOH; $CoAgg^{III}$: Fe^{3+}/H_2O_2, picolinic acid, pyridine(/AcOH). For example, see: (a) Barton, D. H. R.; Halley, F.; Ozbalik, N.; Young, E.; Balavoine, G.; Gref, A.; Boivin, J. *New J. Chem.* **1989**, *13*, 177–182; (b) Barton, D. H. R.; Halley, F.; Ozbalik, N.; Schmitt, M.; Young, E.; Balavoine, G. *J. Am. Chem. Soc.* **1989**, *111*, 7144–7149; (c) Barton, D. H. R.; Hu, B.; Li, T.; MacKinnon, J. *Tetrahedron Lett.* **1996**, *37*, 8829–8832; (d) Barton, D. H. R. *Tetrahedron* **1998**, *54*, 5805–5817.
11. Although the intermediate formation of a highly oxidized iron species, which initiates oxidation processes through a non-radical pathway was suggested by Barton, a recent detailed experimental study provided compelling evidence to support the preponderance of hydroxyl and carbon radical chemistry in Gif systems. See: Stavropoulos, P.; Çelenligil-Çetin, R.; Tapper, A. E. *Acc. Chem. Res.* **2001**, *34*, 745–752.
12. The reason for the dissatisfactory results obtained, when $HO^{\bullet}$ was generated under Fenton- or Gif-conditions, is not yet clear. In both cases the reaction mixture is strongly heterogeneous, and it might be supposed that $HO^{\bullet}$, once generated at the surface of the precipitated iron salt, could not escape into the organic phase, where **1** was dissolved.
13. Typical experimental procedure: 13 μmol of **7** and 128 μmol of **1** were mixed in anhydrous acetonitrile (10 mL) in a Pyrex reactor. The dissolved oxygen was removed by ultrasound treatment for 15 min under a steady flow of argon. The mixture was irradiated under argon with a medium-pressure mercury lamp and analyzed by GC using *n*-hexadecane as internal standard. Product identification was performed using authentic samples of **5** and **6**.[6a,e] GC: (a) Varian CP 3380, column CP-Sil 5 CB, 30 m, $100_5 \rightarrow 200_{15}$, heating rate 5°C min^{-1}; (b) Varian GC 3300, column OV 1701, 25 m, temperature program see (a). GC–MS: Finnigan MAT 8200, Varian 3700; column Optima 1, 30 m, 80→250, heating rate 10°C min^{-1}.
14. It was verified that no reaction between the radical precursor **7** and **1** occurred in the absence of light.
15. The compound **9** has a higher stability towards visible light, which makes it easier to handle. See: (a) Hartung, J. *Eur. J. Org. Chem.* **2001**, 619–632; (b) Adam, W.; Hartung, J.; Hideki, O.; Saha-Möller, C.-R.; Špehar, K. *Photochem. Photobiol.* **2000**, *72*, 619–624.
16. No attempt was made to identify the possible byproducts under these conditions.
17. The exclusive formation of the *cis* fused bicyclic ketones **5** and **6** could be explained by the steric constraints occurring during the cyclization step **3**→**4** and was verified by us in an earlier work by semi-empirical calculations.[6a]
18. The structure of compound **16** was verified using an authentic sample.[6b]